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Ionic Liquids in Organic Synthesis

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Ionic Liquids in Organic Synthesis

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Preface

Ionic liquids have received a great deal of interest in the past decade. The rapid growth is evident from the number of papers published in this field. A fairly large percentage of these publications are from organic chemists who have recognized the potential of these liquids as viable medium for organic reactions. The chapters in this book are based on papers presented at the special symposium titled *Ionic Liquids in Organic Synthesis* held at the 228th National Meeting of the American Chemical Society (ACS) at Philadelphia, Pennsylvania during August 24–28, 2004. This symposium was the first international meeting focusing primarily on the applications of ionic liquids in organic synthesis. The objective of the symposium was to provide a forum to bring chemists together to review the status and promise of these materials for organic reactions. Also, with the same spirit this book has been produced in the hope that industrial chemists would take examples reported in each chapter and join the effort to find practical synthetic applications of ionic liquids, because their active participation is crucial to advance the field of ionic liquids from academic curiosity to practical reality. The chapters contributed in this monograph are from presenters at the sympoium and also few others who have made significant contribution in the field of ionic liquids.

The symposium would not have been successful without invaluable support from the following academic, industrial and professional organizations. The symposium was hosted and sponsored by the organic division of the ACS. Additional financial support was received from the Ne ' Jersey Institute of Technology, and the ACS Petroleum Research Fund. The industrial support was received from Merck KGaA/EMD Chemicals, SACHEM, Rohm

and Haas, GFS Chemicals, BASF, Strem Chemicals, and Sorbent Technologies. I am indebted to all who supported the symposium and to the authors who contributed to this book and I look forward to continue to work with them.

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Chapter 1

The Interactions Affecting Organic Reactivity and Selectivity in Ionic Liquids

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Ionic liquids are emerging as novel replacements for volatile organic compounds traditionally used as industrial solvents: however, little is known about how the use of an ionic liquid can affect the reactions of solute species. With their unique properties, ionic liquids may really induce significant solvent effects on a wide range of processes. In this paper, the solvent properties of ionic liquids are discussed at the light of kinetic and stereochemical studies recently performed in our laboratories on some typical organic reactions.

Introduction

Chemical reactivity in solution is mainly determined by the ability of the solvent to interact with substrates, intermediates, transition states (1). The key properties of a solvent are therefore those that determine this interaction. For molecular solvents, these properties are recorded as "polarity". The polarity of a molecular solvent is commonly expressed by its dielectric constant, although this parameter is frequently unable to provide adequate correlations with many experimental data.

Ionic Liquids (ILs) can be classified, in analogy with the other solvents, on the basis of their bulk physical constants (2, but at variance with molecular

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solvents, dielectric constants cannot be directly measured. Actually, solvent polarity can be expressed also by other physico-chemical constants and several polarity scales, based on solvatochromic measurements, partition methods and kinetic measurements, have been developed in the last century to classify molecular solvents (1).

Solvatochromic dyes and partition methods have been recently used to determine ILs polarity and applying multiparameter equations, able to quantify independently the variety of solvent-solute interactions, dipolarity/polarizability, H-bond acidity and H-bond basicity of several ionic liquids have been determined (3). At variance, no systematic study has been performed to determine ILs polarity through the well-known quantitative theories of solvent effect on reaction rates.

Recently, we have tried to obtain information about the ability of ionic liquids to affect organic reactivity and catalyzed processes performing stereochemical and kinetic studies of simple organic reactions (4). In agreement with the data arising from solvatochromic and partition measurements, these studies have evidenced that ILs not only have a high polarizability/dipolarity but also a structure dependent H-bond donor ability, which significantly can affect the organic reactivity. On the other hand, organic reactivity depends even by other peculiar properties of ILs, such as the high cohesive pressure and the high order degree.

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Ionic liquids effects on electronic transitions of dipolar dyes: the reaction field approach

Solvent effects on solute structure, reactivity and properties are important aspects of solution chemistry. One key approach to understand solvent effects is solvatochromism, *i.e.* the solvent induced changes in the electronic transitions of solutes (5).

Numerous methods for describing solvatochromism in terms of solvent characteristics have been proposed. One simple approach consists in characterizing these effects in terms of an empirical polarity scale which is generally based on spectral data from a single molecule (1). These "single point" measurements have been recently applied to investigate the "polarity" of ILs. (6). Although the polarity scales obtained using different probes show some inconsistencies, they generally suggest that ILs polarity is similar to short chain alkyl alcohols. More in particular, the $E_T(30)$ scale has evidenced that for the 1-alkyl-3-methylimidazolium ILs the alkyl chain length practically do not affect E_T^N values, which are similar to ethanol (E_T^N = 0.65), but the introduction of a methyl at C-2 reduces the solvent polarity (7). This behaviour is in agreement with the extensively discussed ability of the proton at C-2 of the imidazolium salts to give hydrogen bonding and with the presumption that changes in E_T^N values are dominated by the hydrogen bonding acidity of the solvent. The values of 1,2,3-trialkylimidazolium ILs are similar to those characterizing the pyrrolidinium salts and not very far from the value

reported for acetonitrile (E_T^N = 0.47). The implicit assumption of this method ("single point" analysis) is that the transition energy of a given probe in a variety of solvents displays a linear dependence with a single parameter. Since a wide variety of solute-solvent interactions (both specific and nonspecific) may be responsible for the solvent effects on the properties of a solute, multiparameter equations have been developed (1). These equations should be able to quantify independently all the possible interactions. In particular, the empirical solvatochromic method developed and refined (8) by Kamlet-Abbaud-Taft (KAT), has been widely used to determine molecular solvents polarity and recently this classical approach has been applied (9) also to ILs. By means of a three terms equation (eq 1) it has been shown that: 1) the dipolarity/polarizability (π*) of these salts is higher than that of alkyl chain alcohols and very similar for all investigated ILs; 2) the H-bond basicity covers instead a large range, from acetonitrile to lower β values, being dominated by the anion; 3) the H-bond acidity (α) is determined by the cation, even if a smaller anion effect may be evidenced. A strong anion cation interaction reduces the ability of the cation to hydrogen bond the substrate.

$$X = X_0 + a\alpha + b\beta + s\pi^* \qquad (1)$$

The third usual approach to evaluate solvent polarity is the reaction field (10), which is based on a dielectric continuum model and contain (in principle) no adjustable parameter. From a theoretical standpoint, the reaction field model of solute-solvent interactions, introduced by Onsager (eq 2), is the simplest to use. In this model a neutral molecule is considered as a sphere of isotropic polarizability α and central point dipole moment μ. The magnitude and direction of the shift in transition energy from that in the gas phase are determined by the dielectric constant (ε_0) and refraction index (n) of the solvent, and by the ground and the excited-state dipole moments (μ) of the solute and by the radius (a) of the (assumed spherical) solvent cavity.

$$E_{1-2} = -\frac{\mu_g(\mu_e - \mu_g)}{a^3}\left[f(\varepsilon) - f(n^2)\right]_{1-2} \qquad (2)$$

$$f(\varepsilon) = \text{Onsager} - \text{function} = 2(\varepsilon - 1)/(2\varepsilon + 1)$$

Generally, the KAT solvatochromic method provides (11) a better description of the solvent effects on the absorption and emission spectra of proper dyes than does the reaction field model. However, recent studies have evidenced (12) that, depending on the probe, the reaction field model may provide a fit equal or superior to the single point (E_T^N) or KAT model. In particular, the differences in the quality of the fits decrease and the validity of the field model increases using probes that have a low hydrogen-accepting ability (12).

Therefore, considering that the application of the reaction field model to ILs could provide an indirect evaluation of the dielectric constants of these solvents, a parameter not available through conventional measurements, we have analyzed the

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solvatochromism of several solutes in ILs and molecular solvents in terms of this model.

Equation 2 presents two solvent physical parameters: the dielectric constant and the refraction index. The dependence of the solvatochromic effect from the refraction index, considering the small variation of this parameter among the different solvents, can be however neglected. The correlation between the probe absorption maximum and the dielectric constant can be therefore expressed in term of a simple linear relation (eq 3):

$$\lambda = A\, f^{1}(\varepsilon) + B \qquad (3)$$

where A is a constant incorporating all the solute related parameters (dipole, cavity radius) and B is the solvent independent contribution to the absorption wavelength. As equation 2, eq 3 is valid exclusively in the absence of specific solute-solvent interactions, like hydrogen bonding.

It is to note that, if the values of A and B are obtained by fitting procedures using conventional molecular solvents, for which dielectric constants are known, eq 3 can be used to estimate the dielectric constants of ILs.

The results related to the application of eq 3 to the solvatochromism of three different probes (Reichardt's dye, quinoline and N,N'-diethyl-4-nitroaniline) are reported in Table 1, 2 and 3, while Table 4 reports the values of A and B found using each probe.

Considering the limited number of conventional solvents used for the fitting procedures, in particular in the case of quinoline, probably the calculated dielectric constants are to be considered semi-quantitative or qualitative evaluations of the true dielectric constants. It is however worth of note that, with few exceptions, the investigated ILs show calculated ε values ranging from 8 to 23. Therefore, the relative permittivity of ILs seems to be not very high, in this interval we can found molecular solvents such as dichloromethane, acetone and 2-propanol. Moreover, a more careful analysis of the data evidences that for each IL the highest value has been found using the Reichardt's dye, a probe able to give specific interactions and consequently more prone to overestimate the ε values. Since eq 3 should be rigorously valid only in the presence of no-specific solute-solvent interactions the best probe for this kind of analysis should be quinoline. Unfortunately, this compound presents an absorption band very close to the absorption of many common ILs and therefore only few salts have been investigated using this solvatochromic dye. Quinoline gives however quite low and very similar dielectric constants for all the investigated ILs. Although in principle the ILs reported in Table 2 might have very similar dielectric constants, we cannot exclude that this behavior is a consequence of the fact that quinoline in ILs does not give true solutions but, in agreement with other aromatic compounds, liquid chlatrate phases.

Further studies are therefore in progress to elucidate the reliability of this classic solvent polarity index in the case of ILs.

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Table 1. Dielectric Constants Calculated from Solvatochromism of Reichardt's Dye in Ionic Liquids

Ionic Liquid	λ_{max} (nm)	ε
$[EtNH_3][NO_3]$	464.06	62.46
$[bmim][PF_6]$	543.96	21.98
$[omim][PF_6]$	558.00	19.73
$[emim][Tf_2N]$	538.92	22.92
$[bmim][Tf_2N]$	553.92	20.34
$[hmim][Tf_2N]$	551.29	20.25
$[omim][Tf_2N]$	599.00	20.75
$[bm_2im][Tf_2N]$	590.84	15.92
$[HO(CH_2)_2mim][Tf_2N]$	470.00	54.94
$[CH_3O(CH_2)_2mim][Tf_2N]$	528.60	25.11
$[BPy][Tf_2N]$	553.53	20.44
$[bmpyrr][Tf_2N]$	591.70	15.85
$[bmim][BF_4]$	545.00	21.80
$[omim][BF_4]$	592.00	15.82
$[bm_2im][BF_4]$	579.23	17.09
$[bmim][SbF_6]$	544.60	21.87
[bmim][OTf]	550.36	20.90
$[emim][N(CN)_2]$	55274	20.52

Table 2. Dielectric Constants Calculated from Solvatochromism of Quinoline in Ionic Liquids

Ionic Liquid	λ_{max} (nm)	ε
$[bmim][PF_6]$	272.17	9.85
$[bmim][Tf_2N]$	273.04	10.83
$[hmim][Tf_2N]$	270.24	8.19
$[bm_2im][Tf_2N]$	272.17	9.85

Table 3. Dielectric Constants Calculated from Solvatochromism N,N-Diethyl-4-nitroaniline in Ionic Liquids.

Ionic Liquid	λ_{max} (nm)	ε
$[EtNH_3][NO_3]$	417.0	17.16
$[bmim][PF_6]$	411.67	10.16
$[emim][Tf_2N]$	409.73	8.85
$[bmim][Tf_2N]$	409.36	8.64
$[hmim][Tf_2N]$	409.23	8,56
$[bm_2im][Tf_2N]$	411.07	9.71
$[bmpyrr][Tf_2N]$	408.42	8.14
$[bmim][BF_4]$	413.43	11.74
$[bm_2im][BF_4]$	404.79	6.66
$[bmim][SbF_6]$	413.05	11.36
[bmim][OTf]	411.20	9.81

Table 4. Values of Parameters A and B Obtained from Least Squares Fitting Procedures to Eq 3 using Molecular Solvents.

Solvatochromic Probe	A (nm)	B (nm)
Quinoline	0.0242	-6.655
Reichardt's Dye	0.0004	1.1552
N,N-Diethyl-4-nitroaniline	0.0075	-2.1974

Simultaneously, we have tried (13) to obtain the same information using another classical approach, investigating the keto-enol equilibrium of 2-nitrocyclohexanone. On the basis of the equilibrium constants determined at several temperatures and on the solvatochromic shift of the absorption band of the enol form it has been possible to isolate the contribution of the aspecific electrostatic effects, F(ε), of specific electrostatic effects (T_N) and the cavitation effects, δ^2. It is noteworthy that also using this approach the ε values found for the investigated ILs ($[bmim][PF_6]$, [emim], [bmim], $[bm_2im]$ and $[hmim][Tf_2N]$) are quite low (ranging from 10 to 22). The data furthermore evidence that cavitation effects play generally an important role in the IL-solute interactions, and these effects are particularly significant in the case of $[bmim][PF_6]$.

Effect of ILs "Polarity" on Reactions Occurring through Dipolar Transition States

Although one of the classical methods to determine the microscopic physical properties of a solvent is to quantitatively measure the ability of the medium to affect the organic reactivity, only few kinetic data have been reported (2a, 14,15)

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for reactions carried out in ILs, at least in comparison with the whole number of papers published on ionic liquids. Recently we have tried to obtain this kind of information investigating the stereochemical and kinetic behaviour of some typical organic reactions occurring through dipolar transition states, in particular, electrophilic additions to alkenes and alkynes (4) and nucleophilic substitution reactions (16). The study of these reactions could give information not only on the ability of ILs to affect reaction rates but also on their attitude to modify the reaction mechanism, affecting the nature and/or the lifetime of the ionic intermediates.

To this aim we have chosen as reaction media some ILs for which the above mentioned methods evidenced a different ability to give non-specific and specific interactions; i.e. ILs having different calculated dielectric constants, cohesive pressures, different dipolarity/polarizability, hydrogen bonding donor and acceptor ability.

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ILs Effects on Mechanism and Stereochemistry of Organic Reactions

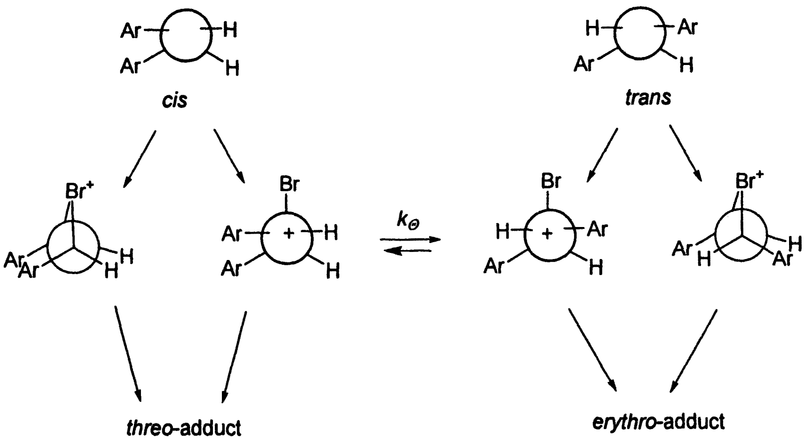
It is well known that the stereochemical outcome of a nucleophilic substitution at a saturated carbon, as well as of an electrophilic addition to a carbon-carbon double bond, is a function of the reaction mechanism that, in turn, can depend on the solvent. Distinctions between mechanisms of chemical reactions in solution are concerned in large part with the sequence in which reactants are assembled and dispersed in relation to bond-making and –breaking steps, and this feature is affected by the solvent.

For nucleophilic substitution reactions, it has been suggested that a clear-cut distinction between reaction mechanisms is not possible and it is more correct to consider a gradual transformation, for example, of an S_N2 to and S_N1 with no sharp borderline as the transition state develops more carbenium ion character (17). The mechanism changes observed as the structures of the reactants or the reaction conditions are modified may be attributed not only to the possibility that two mechanisms can exist concurrently, but also to the fact that a mechanism become the other (18). In particular, it has been stated that this transformation can take place when the intermediate in a stepwise mechanism become less stable, so that it disappears and the reaction become concerted (18). The lifetime of the intermediate, rather than the character of the transition state has been therefore considered an important criterion for a clear distinction between nucleophilic substitution mechanisms (18).

Also in the case of electrophilic addition reactions (electrophilic bromination of aryl substituted olefins) the lifetime of the ionic intermediate has been considered the main factor affecting the dependence of the stereochemistry on solvent (19).

Both nucleophilic substitutions (15,16) and electrophilic addition[4] reactions have been investigated in ILs. Dihaloalkenes and dihaloalkanes have been obtained in high yield and high stereoselectivity by addition of halogens (Br_2, BrCl, ICl and

IBr) to alkenes and alkynes (4,20). The reactions in ILs give exclusively or preferentially the *anti* addition products, and the stereospecificity of the addition process is generally higher than that characterizing the same reactions in chlorinated solvents, also when carbenium ions are involved (for example in the case of bromine addition to *cis*-stilbene and derivatives bearing electrondonating substituents). Since, open β-bromocarbenium ions give the *syn* addition products mainly through an attack *anti* of the counter anion, after rotation around the C-C bond (k_θ, in Scheme 1), the stereochemistry of the products obtained in ILs suggests that in these media the intermediates have a reduced lifetime; rotation around the C-C bond is not able to compete with the faster nucleophilic trapping.



Scheme 1

Related to the nucleophilic substitutions, recent studies performed in our laboratories on the reactions of primary, secondary and tertiary halides or tosylates with KCN and NaN_3 (Scheme 2) in [bmim][PF_6], [bmim][Tf_2N] and [hpy][Tf_2N] have evidenced[16] that ILs are able to affect the solvent-dependent spectrum of intermediate mechanisms characterizing these reactions (S_N2-S_N1).

The ability of Cl^-, Br^-, I^- and TsO^- to act as leaving groups in the substitution reaction of primary substrates with NaN_3 is similar to that reported for the same process in cyclohexane, exactly corresponding to that calculated (21) for S_N2 reactions in the gas phase and suggests the absence of strong specific interactions between the examined ILs and the activated complex. However, secondary substrates exhibit a reactivity comparable or higher than that of the corresponding primary substrates and lead to the exclusive formation of the substitution products, with complete inversion of configuration when chiral substrates are used. At variance, relevant amounts of elimination products are generally obtained by reaction of KCN with the same secondary substrates.

The different reactivity of the secondary substrates towards the two nucleophiles (N_3^-, CN^-), excludes a rate determining diffusion controlled trapping

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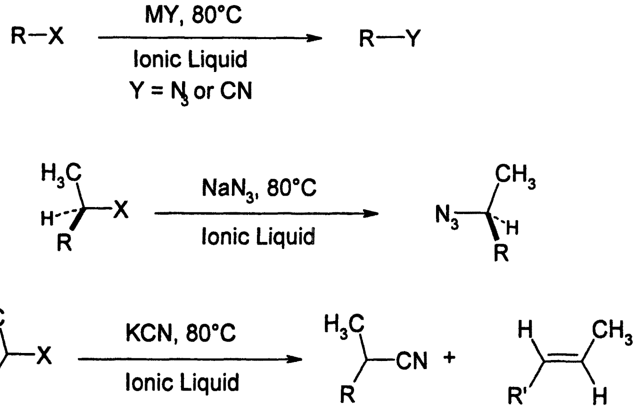
of a free secondary carbocation. Moreover, in agreement with this latter hypothesis: i) no racemization was observed when optically active secondary substrates were used in the reaction with NaN_3; ii) secondary congested substrates (such as 2-bromoadamantane, for which a S_N2 mechanism is precluded by the cage structure) practically do not react with NaN_3 in all the examined ILs.



Scheme 2

To account for the observed reactivity and stereoselectivity of primary, secondary and tertiary substrates a shift of the mechanism from S_N2 to S_N1 has been proposed for the reaction of NaN_3 in ILs. More in particular, it has been hypothesized that the reaction proceeds through the rear-side nucleophilic attack of N_3^- (pure S_N2 mechanism) in the case of primary substrates. This mechanism however gradually shifts towards a pure S_N1, surely occurring in the case of the bridgehead cage 1-iodoadamantane, passing through the nucleophilically assisted formation of an ion pair intermediate in the case of secondary uncaged substrates (Scheme 3).

$$N_3^- + R{-}X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [N_3^- \cdots R{-}X]^- \xrightarrow{k} R{-}N_3 + X^-$$

Scheme 3

Moreover, in agreement with this hypothesis, the reactivity order of 2-bromoheptane with the investigated nucleophiles ($N_3^- >> CN^-$) is opposite to that observed (22) in molecular solvents for displacement reactions on methyl halides (pure S_N2 reactions), but the same as for nucleophilic reactions occurring through carbocations. This behaviour seems therefore to indicate a larger amount of carbenium ion character in the transition state of this secondary substrate, as expected for the formation of a nucleophilically assisted ion pair intermediate.

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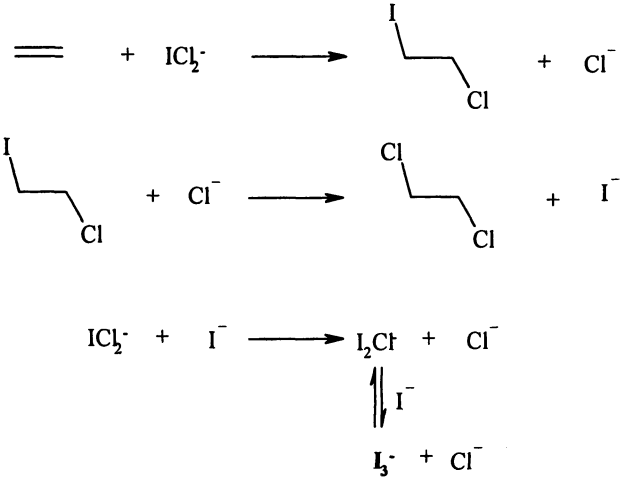
It is worth of note that the shift in the substitution mechanism from S_N1 to S_N2, or the ability of ILs to affect the competition between substitution and elimination, are not the sole mechanisms which can affect products distribution. ILs are also able repress the formation of unwanted by-products. For example, the electrophilic addition of ICl_2^- to olefins in chlorinated solvents is an apparently very slow reaction, which generally gives the expected *anti* addition products in low yields. Recent investigations have shown (4c) that the progressive darkening of the reaction mixtures, observed when the reactions are carried out in molecular solvents (1,2-dichloroethane or dichloromethane), may be attributed to the formation of I_3^-, arising from the reaction of formed chloride anion with the addition products, according to Scheme 4. This unwanted substitution reaction, which leads to the decomposition of the reactant and simultaneously to the formation of dichloro derivatives besides the expected iodo chloroadducts, in ionic liquids does not compete significantly with the addition process. More in particular, this reaction is practically suppressed when the addition of ICl_2^- is performed in ILs having a considerable hydrogen bonding donor ability ([emim] and [bmim][Tf_2N]). A result this latter, which is in agreement with recently reported (15a,b) data on nucleophilic substitution reactions in ionic media showing that the nucleophilicity of the chloride anion in ILs is lower than in chlorinated solvents.



Scheme 4

In agreement with the solvatochromic measurements, kinetic (see below) and products distribution data evidence moreover that the hydrogen-bond donor ability of ILs is controlled by the cation but it is moderated by the ability of the anion to act as H-bond acceptor; as suggested[9] by Welton and co-works, a strong anion-cation interaction reduces the aptitude of the cation to hydrogen bonding the substrate.

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$$[\text{cation}]^+ + [\text{anion}]^- \rightleftharpoons [\text{cation}]\text{-----}[\text{anion}]$$

$$[\text{cation}]^+ + \text{S} \rightleftharpoons \text{S---}[\text{cation}]^+$$

Although in principle, the same interaction should be able to affect also the ability of the anion to interact with substrates or catalysts, only few data have been reported in this connection. We have recently observed (23) that the anion nature has a great influence on the outcome of the Stille reaction: non nucleophilic salts give generally better results and, among the investigated ionic solvents, the reactions in Tf_2N^- salts are characterized by the highest reaction rates. This behaviour has been attributed to the ability of the anion to coordinate the metal (Sn) and favour the transmetallation process, through an increase in the length of the Sn-vinyl bond. It is however worth of note that the experimental data seem to indicate that ability of the anion to interact with the metal is affected by the nature of the cation. A competition between the cation and the Sn atom for the anion, due to the equilibria below reported, has been therefore hypothesized.

$$[\text{cation}]^+ + [\text{anion}]^- \rightleftharpoons [\text{cation}]\text{-----}[\text{anion}]$$

$$[\text{anion}]^- + R_4\text{Sn} \rightleftharpoons R_4\text{Sn---}[\text{anion}]$$

IL Effects on Reaction Rates and Mechanisms

Important information about the solvent properties of ILs have been obtained (4b,c) also investigating the electrophilic addition of trihalide anions (Br_3^-, ICl_2^- and IBr_2^-) to alkenes and alkynes. For these reactions trihalide imidazolium salts have been used as reagent-solvents or as reagents, performing in this latter case the reaction in other ILs. These salts, which can be easily prepared by addition of an halogen (Br_2, ICl or IBr) to an imidazolium (generally [bmim]) halide, give the *anti* addition products with a complete stereospecificity, independently of alkene or alkyne structure. The additions of Br_3^- and ICl_2^- follow a second order rate law suggesting, together with the stereochemical data, concerted mechanisms of the type previously reported for the tribromide addition in molecular solvents. These mechanisms should be characterized by a product- and a rate-determining nucleophilic attack by bromide or chloride on the initially formed alkene or alkyne-halogen π-complex (in Scheme 5 is reported the mechanism for Br_3^- addition to alkynes).

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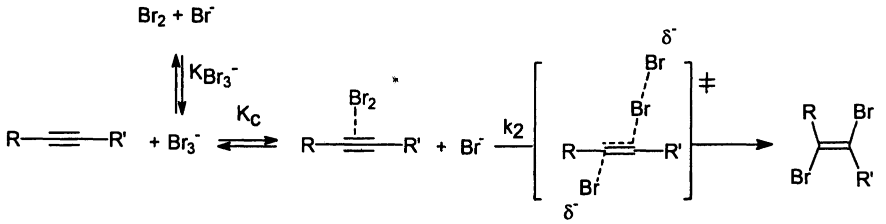
In Ionic Liquids in Organic Synthesis; Malhotra, S.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2007.



Scheme 5

In chlorinated solvents, Br_3^- addition is positively affected by the ability of the medium to give H-bonding. These reactions have been therefore performed in ILs having a different polarity and, more in particular, being characterized by a different ability to give H-bonding. However, at variance with the behaviour observed in chlorinated solvents, the kinetic constants and the activation parameters for the addition of Br_3^- to several alkynes seem to be not affected of this feature. This might be a consequence of the fact that in ILs, at variance with molecular solvents, both bond breaking and bond making are affected by the solvent H-bonding ability. In molecular solvents bond making is not influenced by this solvent feature, being the entering bromide ion present as ion pair with the tetraalkylammonium cation. Considering that in this reaction bond-breaking and bond making probably occur simultaneously in the rate determining transition state only a very little effect, if any, may be detected.

On the other hand, the addition of ICl_2^- is much more affected by the physico-chemical properties of ILs and a possible role of the H-bonding donor ability of IL has been evidenced. In [bmim][Tf_2N], the IL having the relatively higher hydrogen bonding donor ability, the activation enthalpy is strongly reduced, while the $\Delta S^{\neq}$ value is significantly increased. At variance, when the reaction is performed in ILs characterized by cations less suitable to give hydrogen bonding, such as [bm_2im][Tf_2N] and [bpy][Tf_2N], the activation enthalpies significantly increase and activation entropies decrease. Moreover, a high activation enthalpy associated with a low activation entropy has been found in [bmim][PF_6]; *i.e.* in the IL characterized by a lower H-bond donor ability but a high cohesive pressure and by a higher order degree. Also these latter properties seem to affect organic reactivity, mainly through entropic effects.

The different sensitivity of the two addition processes (Br_3^- and ICl_2^-) to the ILs properties suggests finally different transition states. Probably the ICl_2^- addition is characterized by a later transition state, having a greater iodiranium character, and the attack by chloride is not itself the rate determining step. The ability of the IL to give H-bonding can indeed affect the reaction rate only in that case that bond-breaking precedes bond-making.

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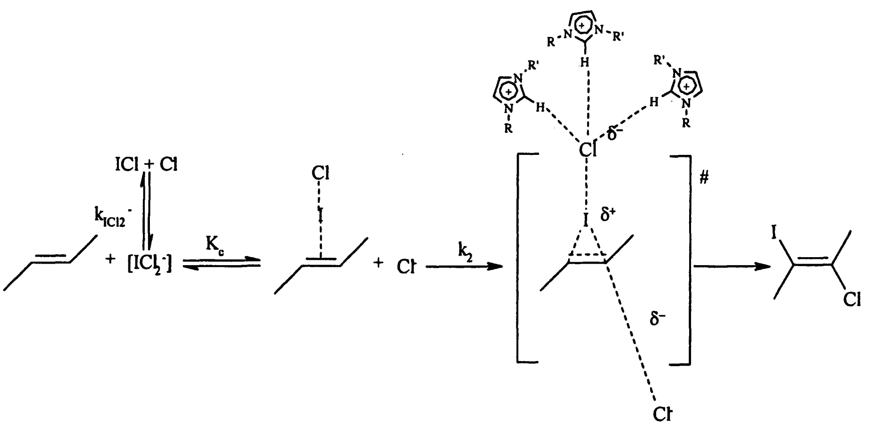
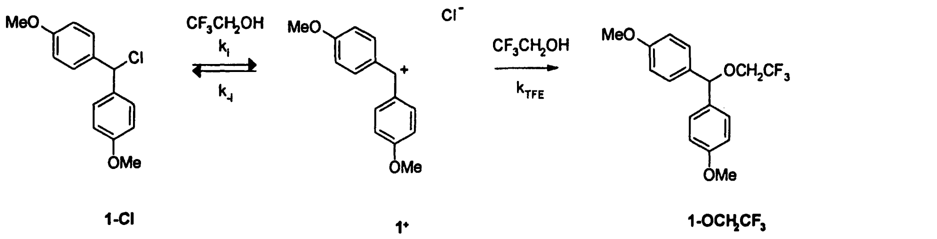


Scheme 6

The ability of ILs to affect the nature and stability of ionic intermediates has been also recently evidenced (24) through the kinetic study of the solvolysis reaction of chloro bis(4-methoxyphenyl)methane (**1-Cl**) in mixtures $[Tf_2N]^-$ based ILs and trifluoroethanol (TFE). In agreement with the behavior characterizing the reaction in CH_3CN/TFE also in IL/TFE mixtures it is possible to observe the immediate formation of the corresponding carbenium ion, $\mathbf{1}^+$, whose absorption band decays following a first order rate law. The kinetic constants (k_{TFE}) measured in TFE/IL mixtures are 5-10 higher than the kinetic constant measured in CH_3CN/TFE.

Considering that, experiments carried out using in the same solvents **1-BF$_4$** as source of carbenium ions give practically the same kinetic constants found using **1-Cl**, it has been assumed that the return of the ionic intermediate ($\mathbf{1}^+Cl^-$) to reagent is not important and, as observed in acetonitrile/TFE, the disappearance of $\mathbf{1}^+$ may be considered a measure of the reaction rate of the cation with the nucleophile (i.e $k_{-i} << k_{TFE}$, Scheme 7).



Scheme 7

The shorter lifetime characterizing the reaction in TFE/IL mixtures may be in principle attributed to an increased electrophilicity of the carbenium ion $\mathbf{1}^+$ in

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these media and/or to a higher nucleophilicity of TFE in the mixtures with ILs. Solvatochromic measurements, prompt to evaluate the solvent properties of the mixtures TFE/IL, and theoretical calculations seem to suggest an increased electrophilicity of the carbenium ion in these media, attributable to a reduced ability of ILs bearing the sterically hindered Tf_2N^- as counteranion to "solvate" the positively charged intermediate, **1**$^+$.

Conclusion

Kinetic and stereochemical studies evidence that the ability of the ILs to affect organic reactivity and selectivity significantly depends on the IL structure.

Good correlation have been found between the activation parameters of simple organic reactions and the solvent parameters arising from other kind of measurements (solvatochromic shifts, equilibria measurements, and so on). Important information about the properties of ILs and on the correlation between structure-solvent properties can be therefore obtained also from kinetic studies of well-known reactions.

Furthermore, the kinetic studies have evidenced that not only the different H-bond ability of ILs can affect reactivity but the reaction rate may be also influenced by the different cohesive pressure and the different order degree.

Finally, it is noteworthy that the peculiar ability of ILs to "solvate" reaction intermediates can significantly affect reactivity and selectivity.

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Chapter 2

Electrophilic Chemistry in Ionic Liquids

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Room temperature ionic liquids (ILs), with low nucleophilicity counterions (OTf^-, FSO_3^-, PF_6^- , BF_4^- etc) constitute unique environments for exploring ionic reactions involving electron-deficient intermediates, in particular carbocations and onium ions. Lewis acids that typically show limited or no solubility in regular organic solvents can in many cases be dissolved/immobilized in imidazolium-based ILs. Moreover, these "designer solvents" appear to be ideal media for utilizing onium salts (i.e. diazonium, selectfluor™ etc) as reagents for synthesis because of their increased solubility in ILs as compared to regular organic solvents (onium salt reagents dissolved in onium salt solvents!). Current interest and activity of this laboratory in the ionic liquids area center around their potential application as solvents and as catalysts in fundamentally important electrophilic transformations, specially those that are carried out on large scale in industry such as nitration, alkylation, acylation and fluorination. The present review summarizes our survey studies in aromatic nitration, aromatic fluorination using NF reagents, fluorodediazoniation (Balz-Schiemann reaction), trans-acylation and deacylation of aromatic ketones, and in adamantylation of aromatics.

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Electrophilic Nitration of Aromatics in IL Solvents: A search for "greener", more environmentally acceptable, methods to carry out acid-catalyzed electrophilic aromatic nitration is certainly worthwhile, given the importance of the process and the demand for nitroaromatics as key organic intermediates.

Despite the fact that aromatic nitration is a very extensively studied area in preparative and mechanistic organic chemistry, there is plenty of room for improvement, in particular with respect to environmental aspects (acid neutralization, aqueous work-up, disposal etc). In this frame of mind, we conducted a survey study to determine the efficacy of arene nitration in various IL solvents (1).

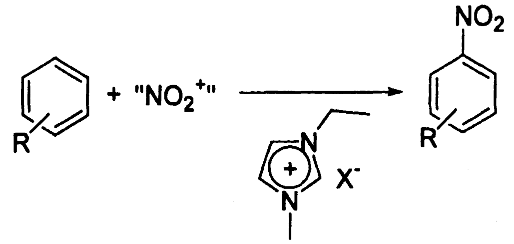

Figure 1. Electrophilic Nitration in imidazolium ILs (Adapted from reference 1.)

The RTILs employed were [EMIM][OTf], [EMIM][CF_3COO], as well as [$HNEtPr^i_2$][CF_3COO]. Nitration reactions with nitronium salts, isoamyl nitrate/TfOH (or isoamyl nitrate/$BF_3.Et_2O$), NH_4NO_3/TFAA, as well as $AgNO_3$/Tf_2O were examined. The most promising systems for nitration in IL solvents are sketched in Scheme 1. As part of the survey study, viable recycling/regeneration protocols were investigated for the identified optimal processes (1).

Table 1 gives a condensed summary together with the yields and isomer distributions.

More recently, Handy and Egrie (2) reported on some other methods for nitration in IL solvents. For example, they used $Yb(OTf)_3$ with HNO_3 and $Cu(OTf)_2$ with HNO_3 as nitrating system, employing N-butyl-N-methylpyrrolidinium triflimide as the ionic liquid.

Qiao and Yokoyama (3) used the Bronsted acidic ionic liquid N-methylimidazolium-N-(CH_2)n-SO_3H in combination with HNO_3 to nitrate benzene, toluene, chlorobenzene and bromobenzene.

Earle et al (4) discovered that in reaction of toluene with HNO_3 employing [bmim][X] ILs the choice of the counterion greatly influenced the reaction outcome. With [bmim][OTf], ring nitration was observed whereas with [bmim][halide] the outcome was ring halogenation and with [BMIM][OMs] side chain oxidation was observed.

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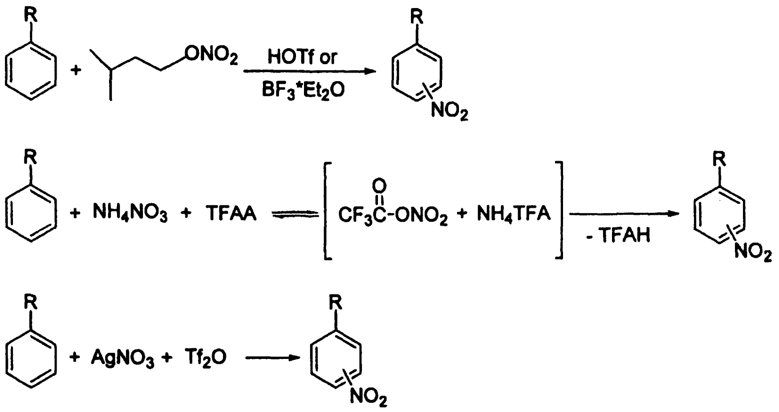

Scheme 1. Most promising nitrating systems for IL nitration of arenes (Adapted from reference 1.)

Electrophilic Fluorination of Arenes with Selectfluor™ (F-TEDA-BF_4) in Ionic Liquids

As was pointed out earlier in the chapter, one of the promising aspects of IL chemistry from our perpective is to increase the synthetic utility of onium salts in preparative chemistry.

The NF-fluorinating agent F-TEDA-BF_4 dication salt dissolves in [EMIM][OTf], [EMIM][BF_4], [BMIM][PF_6] and [BMIM][BF_4] (assisted by sonication). The resulting systems are convenient media for electrophilic fluorination of arenes under essentially acid-free conditions in a simple set-up which avoids the use of volatile organic solvents. The process requires a simple extractions procedure and no aqueous work-up, and it offers the possibility to recycle and reuse the IL (5).

Representative examples are gathered in Tables 2-4. For comparison, anisole was fluorinated with Selectfluor™ in recycled [EMIM][OTf] (see Table 2).

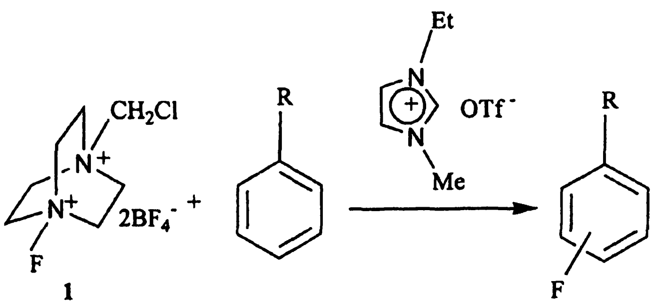

Figure 2. Fluorination of aromatics with Selectfluor (Adapted from reference 5.)

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Table 1. Nitration of Arenes in Ionic Liquids[a]
(Adapted from reference 1.)

R-Ar	*Ionic Liquid.*	*Yield(%)*	*Isomer distribution (%*
OMe	[emin][OTf]	95 (GC)	67.1/-/32.9 (GC)[b]
	[emim][CF_eCOO]	75 (NMR)	64.5/-/35.5 (NMR)[b]
	[HNEtPr$^1_2$][CF_3COO]	99 (NMR)	74.3/-/25.7 (GC)[b]
1-MeO/4-Me	[emim][OTf]	90 (GC)	100[c]
	[emin][CF_3COO]	70 (GC)	100[c]
	[HNEtPr$^1_2$][CF_3COO]	88 (GC)	100[c]
tBu	[emin][OTf]	80 (GC)	12.1/7.5/80.4
	[emin][CF_3COO]	81 (GC)	7.9/6.8/85.3[b]
	[HNEtPr$^1_2$][CF_3COO]	64 (GC)	8.4/6.2/85.4
1,3,5-tri-Me	[emin][OTf]	80 (NMR)	
	[emin][CF_3COO]	>66 (NMR)	
	[HNEtPr$^1_2$][CF_3COO]	53 (NMR)	
F	[emin][OTf]	90 (GC)	9.4/3.2/87/4 (GC)[b]
	[emin][CF_3COO]	54 (GC)	6.6/-93.4 (GC)[b]
	[HNEtPr$^1_2$][CF_3COO]	97 (GC)	3.8/3.4/928 (GC)[b]
Me	[emim][CF_3COO]	65	49.5/2.0/48.5 (GC)[b]
	[emin][OTf]	60	59.0/2.1/39.9 (GC)[b]
	[HNEtPr$^1_2$][CF_3COO]	58 (NMR)	54.03/3.6/42.4(GC)[b]
H	[emim][CF_3COO]	50 (GC)	
	[emim][OTf]	84 (GC)	
	[HNEtPr$^1_2$][CF_3COO]	56 (GC)	
CF_3	[emim][CF_3COO]	~3 (GC)	14.8/66.8/18.4 (GC)[b]
	[emim][OTf]	24 (GC)	9.3/89.2/1.5 (GC)[b]
4-F/1-Me	[emim][OTf]	57 (NMR)	13.0/79.1/7.9 (GC)[d]
	[emim][CF_3COO]	<56[e]	9.9/3.9/86.2 (GC)[d]
[HNEtPr$^1_2$][CF_3COO]	42-62 (GC)	27.5/42.5/30.0 (GC)	17.7/15.0/62.3 (GC)[f]
NO_2	[emin][CF_3COO]	----	----
	[emim][OTf]	----	----
naphthalene	[emin][CF_3COO]	100 (GC)	92.9/7.1 (GC)[g]

[a]For [emin][OTf], the nitration system was isoamyl nitrate/TfOH. For [emin][CF_3COO] and [HNEtPr$^1_2$][CF_3COO], the nitration system was NH_4NO_3/TFAA. [b]Ortho-/meta-/para-, [c]4-Methyl-2-nitroanisole. [d]3-Nitro- and 2-nitro-4-F-toluene plus a skeletally rearranged fluoronitrotoluene isomer. [e]Small impurity present. [f]Rearrangement increases with increased reaction times. [g]1-Nitro/2-nitro.

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Table 2. Electrophilic fluorination of anisole with the NF-reagents in ionic liquid solvents *(Adapted from reference 5.)*

Ionic liquid	ArH : NF ratio (molar ratio)	Yield (%) [a] NMR	GC	Isomer distribution (%) NMR[b] ortho-	para-	GC ortho-	para-
		F-TEDA-BF_4 (1)					
[emim][CF_3SO_3]	9 : 1	53	56	47	53	*	*
recycled once	10 : 1	41	36	48	52	*	*
recycled twice	11 : 1	45	46	47	53	*	*
recycled 3[rd] time	11 : 1	42	40	46	54	*	*
[emim][BF_4]	10 : 1	37	42	43	57	*	*
[bmim][PF_6]	12 : 1	43	39	48	52	*	*

[a)] Yields for fluorinated products were determined from ^{1}H NMR and GC using mesitylene as internal standard. [b)] Determined from ^{1}H NMR spectra. [c)] Determined from ^{19}F NMR spectra. *Incomplete GC peak separation for anisole and 4-fluoroanisole.

Fluorodediazoniation in Ionic Liquid Solvents

The classical Balz-Schiemann reaction is a widely used process for replaceing the diazonium group by fluorine. The original procedure has reproducibility problems and the yields are variable depending on the arene substrates. A number of modifications to the original procedure have been devised (6). In the context of onium ion chemistry in ionic liquids, we studied this reaction in room temperature imidazolium ILs (7). Diazonium salts dissolve in imidazolium ionic liquids, and subsequent heating produces the fluoroaromatics in high yields (Figure 3).

Alternatively, it is possible to combine diazotization and fluoro-dediazoniation into a one-pot process (7) (Figure 4).

Transacetylation and Deacetylation in Ionic Liquid Solvents

The transacetylation is the reverse of Friedel-Crafts acylation reaction. It is an acid-catalyzed process in which the acyl group is transferred from an aromatic ketone to an activated aromatic substrate which is typically used in excess (Figure 5). The reaction is greatly facilitated by the presence of ortho alkyl

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Table 3. Electrophilic fluorination of ArH with F-TEDA-BF_4
(Adapted from reference 5.)

ArH	Ionic liquid	ArH : NF (molar ratio)	Yield (%)* NMR	Yield (%)* GC	Composition of reaction mixture (%)
p-Methyl-	[emim][CF_3SO_3]	4 : 1	56	46[b]	2-fluoro-4-methylanisole (93) 3-fluoro-4-methylanisole (6) 2,6-difluoro-4-methylanisole (1)[c]
p-Chloro-anisole	[emim][CF_3SO_3]	5 : 1	50	50[b]	2-fluoro-4-chloroanisole (95) 2,6-difluoro-4-chloroanisole (5)[c]
p-Fluoro-anisole	[emim][CF_3SO_3]	4 : 1	24	22	2,4-difluoroanisole (-100)
p-Xylene	[emim][BF_4]	10 : 1	24	21[b,c]	2-fluoro-1,4-dimethylbenzene(~100)
p-Xylene	[emim][CF_3SO_3]	10 : 1	51[d]	46[b,d]	2-fluoro-1,4-dimethylbenzene(~100)
Mesitylene	[bmim][PF_6]	4 : 1	52[e]	50[b,c]	2-fluoromesitylene (~100)
p-Nitro-toluene	[bmim][BF_4]	4 : 1	<1	0	
p-Nitro-toluene	[bmim][CF_3SO_3]	4 : 1	<1	0	

[a]Yields of fluorinated products were calculated from ^1H NMR and GC using mesitylene as internal standard. [b]No authentic fluorinated sample was available as GC standard. [c]Specific assignment tentative. [d]Yield of 2-fluoro-1,4-dimethyl-benzene after repeating the fluorination reaction in the same reaction vessel by adding a second equivalent of F-TEDA-BF_4. [e]Yield of 2-fluoromesitylene was calculated from ^1H NMR and GC using anisole as internal standard.

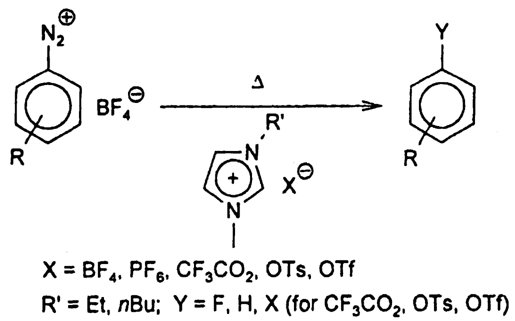

Figure 3. Fluorodediazoniation in ionic liquid solvents
(Adapted from reference 7.)

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Table 4: Electrophilic fluorination of bicyclic and polycyclic aromatic hydrocarbons with F-TEDA-BF_4 *(Adapted from reference 5.)*

ArH	Ionic liquid	ArH : NF (molar ratio)	Yiled (%)[a] NMR	GC	Composition of reaction mixture (%)[b]
Naphthalene	[emim][CF_3SO_3] (recycled once)	4 : 1	88	*	1-fluoronaphthalene (91) 2-fluoronaphthalene (7) 1,8-difluoronaphthalene[c] (2)
1-Methyl-naphthalene	[bmim][PF_6] (recycled twice)	2 : 1	23	*	1-fluoro-4-methylnaphthalene 2-fluoro-1-metylnaphthalene 5-fluoro-1-methylnaphthalene[c] 1-fluoro-8-methylnaphthalene[c]
Dibenzo-Furan	[emim][CF_3SO_3] (recycled 3-times)	4 : 1	49[d]	38[d,c]	1-fluorodibenzofuran (20, NMR; 18,GC) 2-flurodibenzofuran (41, NMR; 42,GC) 3-fluorodibenzofuran (39, NMR; 40,GC)

[a])Yields of fluorinated products were calculated from ^1H NMR and GC using mesitylene as internal reference. [b])Determined from ^{19}F NMR spectra. [c])Specific assignment tentative. [d])Yields of fluorinated products were calculated from ^1H NMR and GC using 4-fluoroanisole as internal reference. [e])No authentic fluorinated dibenzofuran isomers were available as GC standard. *No isomers separation.

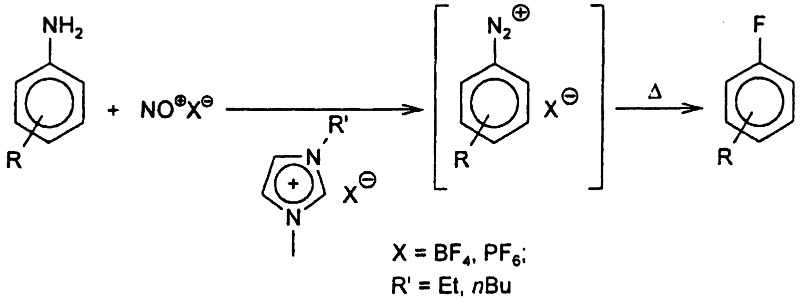

Figure 4. One-pot diazaotization-fluorodediazoniation in IL solvent (Adapted from reference 7.)

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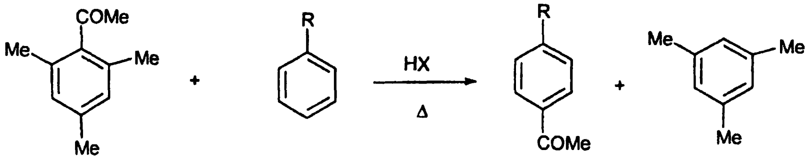

Figure 5. Acid-catalyzed Transacylation (Adapted from reference 10.)

substitutents which force the –COR group out of coplanarity with the ring and weaken the Ar-COR bond.

The key intermediate is the arenium ion of *ipso* attack which is formed under equilibrium conditions. Earlier reports of this reaction employed large excess of $AlCl_3$-HCl at 100°C (8) or boiling TFA (used in large excess) (9). An earlier kinetic study using pentamethylacetopheneone (9) established a 2-step process involving deacetylation with the formation of mixed anhydride which subsequently re-acetylates the arene (anisole).

Using TfOH as catalysts, we developed an ionic liquid version for this chemistry (10) under mild conditions (typically at 70°C) (Figure 6). In the absence of the arene receptor or by increasing the temperature to 100°C the outcome of the reaction can be changed to deacetylation (10). The ketone substrates and the RTILs employed in these reactions are depicted in Figure 7.

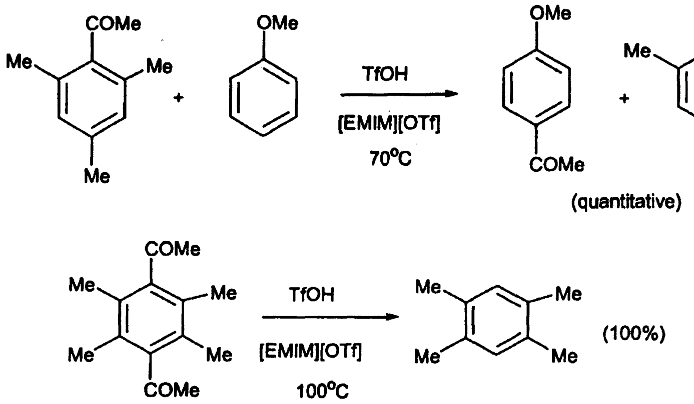

Figure 6. TfOH-catalyzed transacetylation and deacetylation of aromatics in IL solvent (Adapted from reference 10.)

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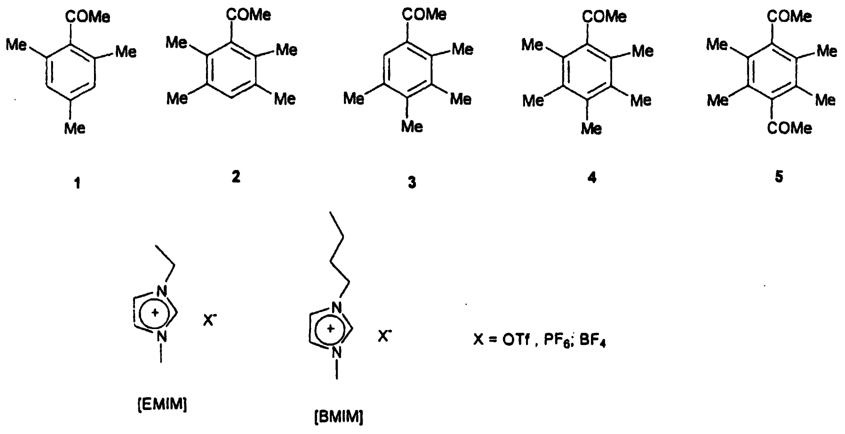

Figure 7. Sterically crowded acetophenones and the ILs used in the study (Aadapted from reference 10.)

The ILs used could be repeatedly recycled and reused (10). For comparison, the data on these reactions are summarized in Tables 5-6 below.

Adamantylation of Aromatics in Ionic Liquid Solvents

The Friedel-Crafts type Adamantantylation of arenes represents a simple one-pot approach for the preparation of various aryladamantanes (Figure 8). Despite its apparent simplicity, this transformation has not been studied in detail, and the synthetic and mechanistic aspects are not very clear. In the context of electrophilic chemistry in IL solvents, we have recently studied this reaction (11) by using [EMIM][OTf] as solvent, TfOH as promoter, and employing 1-AdaOH, 1-AdaCl, 1-AdaBr and 1-Br-3,5,7-trimethyladamantane as adamantylating agents. The synthetic scope of this transformation and the mechanistic details, including a DFT study of the carbocations, have recently been reported in full.

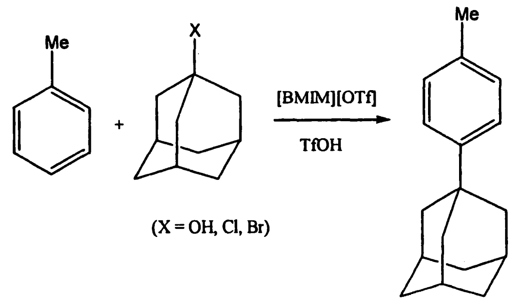

Figure 8. Adamantylation of aromatics in IL Solvents (Adapted from reference 11.)

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Table 5. TfOH-catalyzed transacetylation to arenes by sterically crowded acetophenones in IL solvents *(Adapted from reference 10.)*

Run #	ArCOMe	ArH	ArCOMe : ArH : TfOH (molar ratio)	IL	Rxn time (h)	Composition of Rxn mixture% unreacted ArCOMe	new ArCOMe[a]	Arene formed
1	2	Anisole	1: 8 : 8	[EMIM][BF$_4$]	4	0	98	100
2	2	Anisole	1: 8 : 8	[BMIM][PF$_6$]	4	9	>100	91
3	1	Anisole	1 : 8 : 8	[EMIM][OTf]	5	0	>100	100
4	1	Anisole	1: 8 : 8	[BMIM][PF$_6$]	5	0	>100	100
5	1	Toluene	1: 8 : 4	[BMIM][OTf]	5	15	15	85
6	2	Anisole	1: 4 : 0	[EMIM][OTf]	24	8	98	91
7	3	Anisole	1: 4 : 0	[EMIM][OTf]	24	0	>100	100
8	5	Anisole	1: 4 : 5	[EMIM][OTf]	48	49	46	40
9	5	Anisole	1: 4 : 5	[EMIM][BF$_4$]	48	49	48	45
10	3	Toluene	1: 4 : 4	[EMIM][OTf]	8	11	12	88
11	1	Toluene	1: 8 : 4	[BMIM][OTf]	24	2	20	98
12	5	Anisole	1: 4 : 16	[BMIM][OTf]	24	7	81	92
13	5	Anisole	1: 4 : 6	[BMIM][OTf]	5	53	46	46

[a] for entries marked with >100%, the calculated conversions for the new ketones were between 101-108%. This possibly stems from incomplete deprotonation/Et_2O extraction in earlier runs

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Table 6. TfOH-catalyzed deacetylation of sterically crowded acetophenones in IL solvents *(Adapted from reference 10.)*

Run #	ArCOMe	ArH	ArCOMe : ArH : TfOH (molar ratio)	IL	Rxn time (h)	Composition of Rxn mixture% unreacted ArCOMe	new ArCOMe	Arene formed
1	4	Anisole	1 : 4 : 4	[BMIM][PF_6]	10	8	0	92
2	5	Anisole	1: 4 : 4	[EMIM][OTf]	10	16	0	84
3	5	Anisole	1: 4 : 4	[BMIM][OTf]	10	15	0	85
4	1	Toluene	1: 8 : 4	[BMIM][OTf]	5	47	0	52
5	3	p-Et_2Ph	1 : 8 :4	[EMIM][OTf]	5	44	0	55
6	5	Anisole	1: 8 : 4	[BMIM][OTf]	5	46	0	53
7	5	EtPh	1 : 4 : 4	[EMIM][OTf]	8	38	0	62
8	5	p-Et_2Ph	1: 4 : 8	[BMIM][OTf]	8	14	0	87
9	3	none	1 : 0 : 4	[EMIM][OTf]	5	47	0	52
10	5	none	1 : 0 : 4	[EMIM][OTf]	5	57	0	42
11	5	none	1 : 0 : 8	[BMIM][OTf]	4	2	0	98
12	5	none	1 : 0 : 8	[EMIM][OTf]	5	0	0	100

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Chapter 3

Electropolymerization of Benzene in an Ionic Liquid

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Due to their wide electrochemical windows ionic liquids are ideally suited to electrochemical studies. It is demonstrated in this short article that in the ionic liquid 1-Hexyl-3-methylimidazolium tris(pentafluoroethyl)trifluorophosphate benzene can be well electropolymerized to give polyphenylene. The deposit is electrochemically active and shows a quasireversible electrochemical behavior. It is shortly discussed that ionic liquids might have a certain impact on the fabrication of devices with conducting polymers.

Introduction

Electronically conductive polymers have been intensively studied since 1977 (1). Typical examples are polyacetylene, polypyrrole, polythiophene, poly-p-phenylene, polyaniline and their derivatives, but also many other heterocyclic or aromatic polymers (2). Often these polymers can be prepared by electrochemical oxidation from aqueous or non-aqueous electrolyte solutions containing the respective monomer. They are characterized by a good electrical conductivity combined with a low weight. The conductivity is based on the conjugated π-electron system, and the formation of charge carriers like polarons or bipolarons by doping. There are more than 5000 papers in the literature that are devoted solely to polypyrrole. One reason is surely that it can be made quite easily in aqueous solutions. A common feature of these conducting polymers is

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In Ionic Liquids in Organic Synthesis; Malhotra, S.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2007.

that they show a quasireversible electrochemical behaviour during successive reduction and oxidation cycles. The doping degree of these conducting polymers can be adjusted by proper selection of the electrode potential. The interesting properties of these polymers have led to their use in supercapacitors, sensors, electrochromic devices, light emitting diodes and other ones, to mention a few. Among the conducting polymers poly(para)phenylene (PPP) is very interesting because it is suited for the fabrication of blue organic light emitting diodes (OLED) (3 – 6). However, the electrochemical polymerization of benzene to PPP is still a challenge as water in the solution has to be avoided strictly. Therefore, in the past only solvents like concentrated sulfuric acid (7), liquid SO_2 (8) or liquid HF were feasible for the electropolymerization of benzene. In 1993 ionic liquids based on $AlCl_3$ were employed for the first time for the electropolymerization of benzene (9). Because of side reactions due to chlorine co-evolution during the electropolymerization the quality of the deposits was not satisfying. Ionic liquids are by definition ionic melts with a melting point below 100 °C (10). During the recent 5 years there has been a remarkable progress in the synthesis of ionic liquids, and there are now already several companies on the market from which these new solvents can be purchased. Especially air and water stable ionic liquids have gained a great interest in the recent years, as depending on the liquid high ionic conductivities, negligible vapour pressures and wide electrochemical windows are obtained. These properties are very important for electrochemical studies, and it has been shown that it is possible to electrodeposit nanoscale light metals and semiconductors (11, 12) in them. It should be mentioned here that ionic liquids have already been employed for the electrodeposition of polypyrrole (13) and poly(3,4-ethylenedioxythiophene) (14) as well as a few other ones. In general it is observed that the electrochemical reversibility of the polymers in ionic liquids is excellent.

Experimental

For synthesis and characterization an ionic liquid from Merck KGaA (EMD) was employed: 1-Hexyl-3-methylimidazolium tris(pentafluoroethyl) trifluorophosphate ([HMIm]FAP) was used as a solvent for the electropolymerization of benzene as well as for the electrochemical characterization of the synthesized polymer films. The liquid was dried under vacuum at an elevated temperature of 110 °C under stirring to water contents below 3 ppm prior to use, as determined by Karl-Fischer titration. Benzene (FLUKA > 99,5 %) with a water content below 0,005 % was used without further purification, its concentration in the liquid was 0,2 mol/l (giving a water content below 5 ppm). All experiments were performed in an argon filled glove box (Vacuum Atmospheres OMNILAB) with water and oxygen below 1 ppm. For the electrochemical experiments a PARSTAT

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2263 potentiostat/galvanostat controlled by a PowerCV software was employed. The quartz crystal microbalance studies were performed measuring the electrical admittance curve of a quartz (covered on both sides with microcrystalline platinum) in parallel to the electrochemical experiments with a network analyzer (Agilent E5100A). One side of the quartz served as working electrode. A platinum ring as well as a platinum wire served as counter and reference electrodes, respectively. Prior to each experiment the platinum electrodes were cleaned by heating to red heat in a hydrogen flame. The electrochemical cell was cleaned at room temperature in a mixture of 50/50 v-% concentrated H_2SO_4 and aqueous hydrogen peroxide (30 %) followed by refluxing in pyrogene free water (aqua destillata ad iniectabilia). A high resolution field emission scanning electron microscope (Carl Zeiss DSM 982 Gemini) was utilized to investigate the surface morphology of the polymer film.

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Results and Discussion

Figure 1 shows the electrochemical window of the ionic liquid on poly- and microcrystalline platinum:

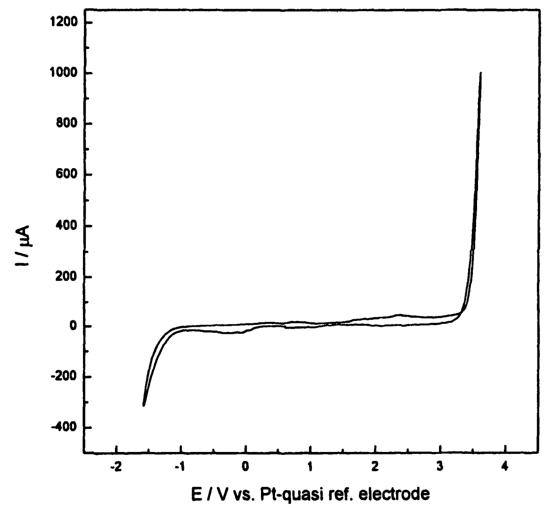

Figure 1. Electrochemical window of 1-hexyl-3-methylimidazolium tris(pentafluoroethyl)trifluorophosphate on platinum

An electrochemical window of a little more than 4 Volt is observed, which in the cathodic regime is limited by the irreversible reduction of the organic cation leading to less defined oligomers. In the anodic regime the electrochemical window is limited by the decomposition of the organic anion. On this electrode potential scale the peak couple ferrocene/ferrocinium is at +500 mV, demonstrating that the anodic decomposition limit of this ionic liquid is about + 3000 mV vs. NHE.

Figure 2 shows 5 successive cycles of potentiodynamic benzene polymerization:

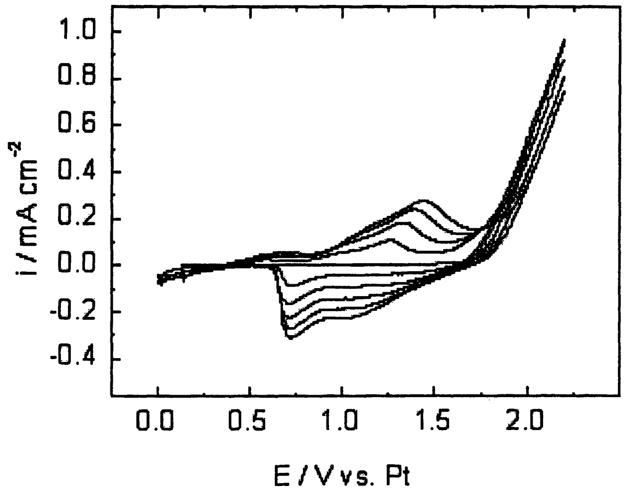

Figure 2. Potentiodynamic electropolymerization of benzene at a scan rate of 10 mV/s, c(benzene) = 0.2 mol/l

In the first scan only capacitive currents flow until an electrode potential of 1.7 Volt. At 1.7 Volt the electrooxidation of benzene starts giving rise to a dark deposit. In the first reduction scan there is a rising cathodic current which peaks at about +750 mV. In the following anodic scan an oxidation current is observed with a peak at about +1250 mV before at +1750 mV a further oxidation of benzene sets in. With a rising number of cycles the reduction and oxidation currents rise, which is typical for a conducting polymer. As was shown elsewhere (15) the peak currents vary almost linearly with the square root of the scan rate indicating diffusion control. However, the wide peak separation is indicative of high overvoltages in the polymer.

In order to determine the degree of doping in the polymer we performed quartz crystal microbalance experiments. Simultaneously with the electro-

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chemical investigations the resonance curve of a platinum covered quartz resonator was measured. Details on this experiment will be reported elsewhere (16). As for all conducting polymers, the charge needed for the formation of the oxidized polymer can be related to the charge needed to build the polymer backbone (2F per mole of benzene), and the charge needed to oxidize the polymer, until it reaches the (potential-dependent) degree of oxidation x. The mass change is due to the effective mass of the benzene rings (76 g per mole of benzene) and the amount of counter anions incorporated into the polymer to compensate for the positive charges within the polymer (445 g * x per mole of benzene). To complicate matters, there can be an additional contribution to mass by trapped ionic liquid. Therefore one can write:

$$\frac{dm}{dQ} = \frac{M_{C_6H_4} + x \bullet M_{anion}}{(2+x) \bullet F} \qquad x = \frac{M_{C_6H_4} - 2F\left(\frac{dm}{dQ}\right)}{F\left(\frac{dm}{dQ}\right) - M_{anion}}$$

if one neglects trapped ionic liquid and

$$\frac{dm}{dQ} = \frac{M_{C_6H_4} + x \bullet M_{anion} + y_{IL} \bullet M_{IL}}{(2+x) \bullet F}$$

$$y_{IL} = \frac{(2+x) \bullet F \bullet \left(\frac{dm}{dQ}\right) - M_{C_6H_4} - x \bullet M_{anion}}{M_{IL}}$$

which allows to calculate the amount of trapped IL if the degree of oxidation x is known. X can be determined easily, as in the experiment we get both the mass of the polymer (determined via the Sauerbrey equation from the frequency shift of the oscillating quartz resonator) and the charge which is needed to fully reduce the synthesized polymer. A typical $\Delta m/\Delta q$ value in the first reduction cycle is 0.002 g/C. With this value we can calculate x. Over all cycles we get values for x between 0,25 and 0,35 which means that in the average a positive charge is delocalized over 3 – 4 benzene rings. It was shown (16) that during reduction and oxidation both anion and cation exchange can take place. With low scan rates mainly anion exchange takes place whereas at higher scan rates also cation

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exchange plays a role. With the known value of x the amount of ionic liquid trapped by the polymer can be estimated. In the average there is one mol of ionic liquid for 5 mol benzene rings.

It should be mentioned here that a commercial quartz crystal microbalance is not suited to measurements in relatively viscous ionic liquids. A self-built device with a frequency analyzer is in any case advantageous as it measures the complex resonance curve of the quartz oscillator.

Finally a high resolution SEM picture is presented in figure 3:

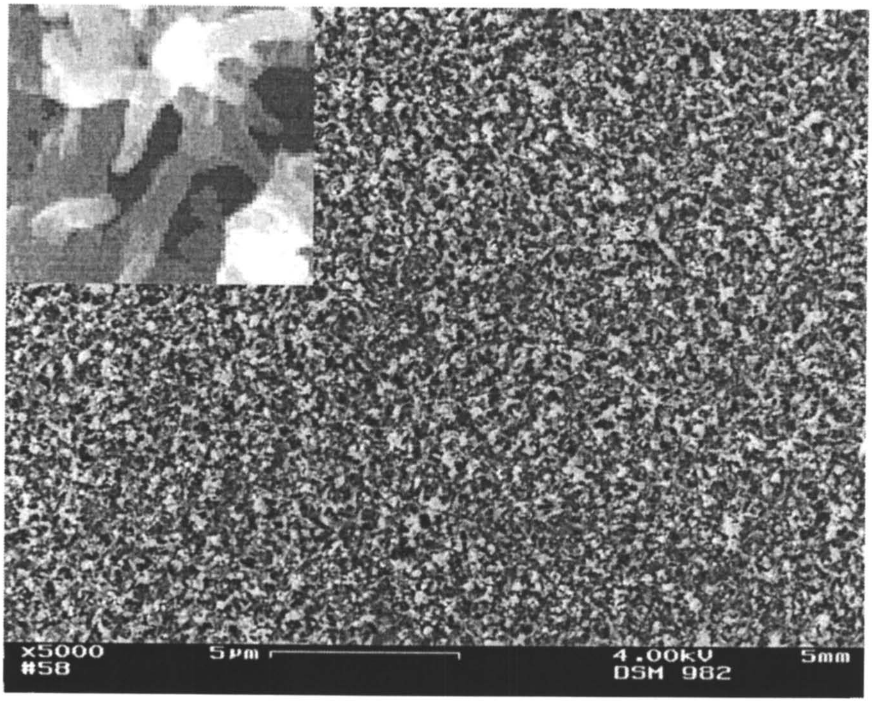

Figure 3. High resolution SEM picture of electropolymerized benzene. The inset shows a 500 nm x 500 nm area

This picture shows that the deposit exhibits an interesting nanoporous structure with smallest structural features in the sub 100 nm regime. It should be mentioned here that in OLEDs the typical thickness of the conducting polymer layer is between 100 and 300 nm. Figure 3 shows the top 500 nm of a several micrometer thick film.

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We have shown in this short contribution that ionic liquids are well suited to the electrodeposition of conducting polymers. On the one hand they have wide electrochemical windows, on the other hand they can be easily made water free which is a basic requirement for the electropolymerization of molecules like benzene, thiophene, styrene and their derivatives. Conducting polymers of these molecules are currently extremely important in the construction of organic light emitting diodes. Maybe an electrochemical process which easily delivers such polymers would open up a new and cheap way in this field.

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Chapter 4

Onium-Poly(Hydrogen Fluorides): Convenient Ionic Liquids for Fluorination and Acid Catalysis

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Onium polyhydrogen fluorides as room temperature ionic liquids (RTILs) have found a wide variety of applications in organic chemistry. They are used as ionic solvents, fluorinating agents and as Bronsted acid catalysts in organic synthesis. A variety of industrially important reactions such as fluorinations, halofluorinations, electrophilic alkylations, nitrations, and hydrocarbon isomerization reactions have been carried out using them. This short review covers some slected salient recent applications of these intriguing ionic liquids.

Introduction

Onium polyhydrogen fluorides such as hydrogen fluoride complexes of amines have been known for over three decades. These complexes are prototypes of the room temperature ionic liquids (RTILs). Although popularized as the environmentally benign solvents only in recent years, RTILs have a long-standing history. Walden reported ethylammonium nitrate (mp 12-14 °C) as the first room temperature ionic liquid, which can be prepared by the reaction of

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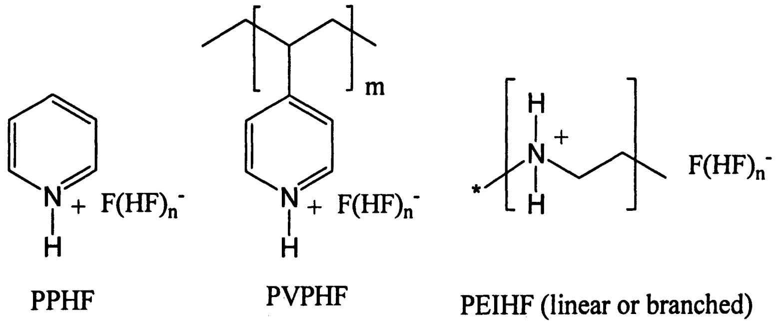
In Ionic Liquids in Organic Synthesis; Malhotra, S.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2007.

ethylamine and nitric acid (*1*). Efforts by Osteryoung and Wilkes in 1970s and Hussey and Seddon in the 1980s have led to a better understanding of the properties of RTILs leading to their applications as green solvents in organic synthesis (*2-6*). Currently there are a wide variety of RTILs involving, for example, salts of organic cations such as tetraalkylammonium, tetraalkylphosphonium, N-alkylpyridinium, 1,3-dialkylimidazolium, and trialkylsulfonium cations (*7-10*).

Whereas anhydrous HF is a gas at ambient temperature (b.p. 19.5 °C) and is highly toxic and corrosive, the amine complexes of HF are relatively nonvolatile, less toxic, and can be handled conveniently. Among a variety of amine-HF complexes known, pyridinium polyhydrogen fluoride (PPHF, Olah's reagent), consisting of 30:70 weight ratio of pyridine and HF, has been extensively applied to a variety of fluorination reactions (*11,12*). The acidity of PPHF is significantly high (H_0 = -11) and is suitable for a variety of acid-catalyzed transformations. Polymer-supported HF complexes have also been prepared and used for fluorination reactions (*13*). Polymeric versions of the reagents, including polyvinylpyridinium polyhydrogen fluoride (PVPHF), and polyethyleneiminium polyhydrogen fluoride (PEIHF) have been developed as alternative reagents for re-use and for convenient handling (*11*). Recently N,N-dialkylimidazolium-$(HF)_{2.3}$ based onium polyhydrogen fluorides have been prepared and used for ring-opening fluorination of epoxides (*14*). The onium-polyhydrogen fluoride complexes are convenient and environmentally benign reagents in organic synthesis. They are also high dielectric constant ionic liquids in their own right.

Recently, dimethyl ether-HF complexes were shown to be stable at room temperature and they can be used in place of PPHF for hydrofluorinations,



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bromofluorinations, and fluorination of alcohols (*15*) In particular, the reagent consisting of the composition with 1:5 weight ratio of DME and HF, DME-5HF, was found to give high yields and selectivities of the fluorinated products. Homologous dialkyl ether-HF complexes (alkyl = ethyl, *n*-propyl) were also found to be useful for fluoroination reactions.

Thermal stabilities of the onium poly(hydrogen fluoride) complexes

The thermal stabilities of the onium poly(hydrogen fluoride) complexes, as defined by their respective threshold volatile temperatue (i.e., the temperature at which the complex loses more than 1% weight), are dependent on the mol ratio of the amine to HF. The higher the ratio of amine:HF, the higher the threshold volatile temperature is. In case of PPHF, for example, the threshold volatile temperature increases from 32 °C to 50 °C as the pyridine to HF weight ratio is varied from 15:85 (py:HF mol ratio = 1:22) to 30:70 (pyrine:HF mol ratio = 1:9) (*16*). The thermal stabilities of the amine-HF complexes do not correlate with the basicities of the amines, as may have been expected from the heat of formation of the $[BH]^+$ F^-. On the other hand, the subsequent step of transferring $[BH]^+$ F^- into the HF solution to give $[BH]^+$ $F(HF)_n$(l) may largely determine the thermal stabilities of the amine-HF complexes (*16*).

Structures of dimethyl ether-HF complexes (DMEPHF)

The structural information for the DME-HF complexes has been probed using ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy, and DFT-based theoretical calculations (*15*). Comparison of the ^{1}H NMR spectra of the complexes with that of the reported dimethyloxonium ion in superacidic media shows that oxonium ions are not involved in the DMEPHF complexes. Whereas sharp ^{19}F NMR signals were observed at 20 °C, at low temperatures (-40 °C to -90 °C), the peaks are considerably broadened indicating the presence of differing acidic protons. The varied chemical shifts, between -40 °C to -90 °C, indicate the freezing of the exchange of the HF molecules between different complexes. DFT-based theoretical calculations (at B3LYP/6-311+G**) indicate a cyclic poly(hydrogen fluoride) bridged structures for DMEPHF. The calculated O-H distances for DME-1HF, is 1.635 A°, which indicates that it is a moderately

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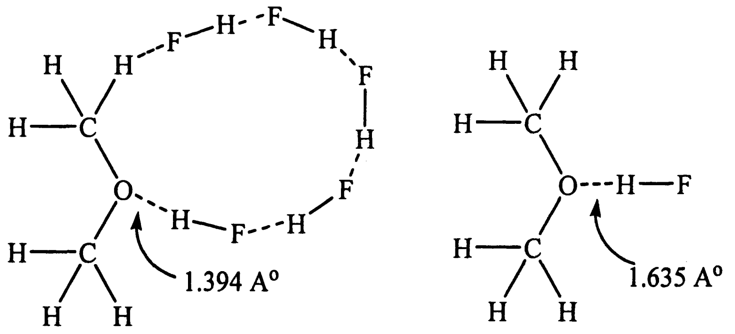
strongly hydrogen bonded complex. Dissociation of HF and DME was calculated to be endothermic by 8.8 kcal/mol. The O-H bond distance gradually decreases as the number of HF molecules in the complex increases, and reaches a value of 1.394 A° for DME-5HF complex. The O-H bond length of the latter structure also is too high and it cannot be considered as an oxonium ion. The proposed cyclic structures are in accord with those suggested for diethyl ether-HF complexes as studied by FT-IR spectroscopy (*17*).



B3LYP/6-311+G** calculated structures for DME-5HF and DME-1HF

Alkylation of isobutane with olefins

Acid-catalyzed alkylation of isobutane with olefins is a process of substantial interest in petroleum industry. Anhydrous HF and concentrated H_2SO_4 are the typically used acid catalysts in petroleum industry. HF-based catalysts have distinct advantages over those of H_2SO_4 as the latter produce large amounts of spent acid and acid-soluble oil. PPHF, which contains a small amount of HF in equilibrium, alleviates the volatility and toxicity problems associated with anhydrous HF (*18,19*). Even though acidity of strictly anhydrous HF was measured to be H_0 = 15.1 by Gillespie, for all practical purposes it is Ho = -11 (i.e., same as that of concentrated H_2SO_4), as it is hygroscopic and is contaminated with slight amount of water (*20*). The PPHF has about nine HF molecules per pyridine and its acidity is comparable to that of regular HF (Ho = -11). Thus it can catalyze alkylation of isobutane with isobutylene to give mostly C_8 and higher alkanes. The research octane numbers

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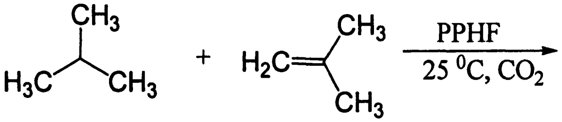
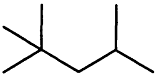
(RON) obtained for PPHF (mol ratio of HF/py = 9:1) catalyzed alkylations are comparable to those obtained by the use of acid catalysts such as triflic acid, and sulfuric acid. The RON numbers are considerable higher when liquid CO_2 is used as a solvent. In liquid CO_2 as solvent, concentrated H_2SO_4 gives a RON of 79.0 whereas PPHF gives a value of 87.0 (*18*).

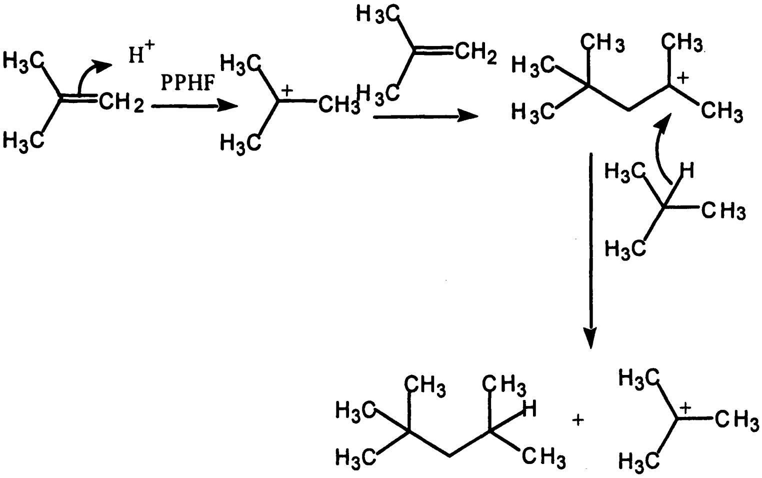


C8 (47.9% + C9 (34.5%)
+ others(7.6%)



Predominant C_9 isomer

A suggested reaction pathway for the alkylation is as follows:



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Thus, PPHF (or anhydrous HF) acts to initiate the reaction by protonation of the olefin. The resultant tertiary carbocation then propagates the chain by electrophilic addition to the olefin to give higher molecular weight carbocation (C_8), which undergoes hydride abstraction from isobutane to give the C_8 alkane regenerating the *tert*- butyl carbocation. It is important to note that at the same time, a variety of side reactions can occur depending on the reaction conditions. The intermediate C_8- carbocationic species can undergo isomerization through sekeletal rearrangements involving hydride and methyl shifts giving various isomeric carbocations, which leads to the formation of C_8-hydrocarbons with differing RON numbers. On the other hand, heavier alkanes can also be formed by further alkylation of the C_8 carbocation to isobutylene. C5- and C6-hydrocarbons are also formed through the cleavage of the C_8- or higher carbocations involving β-scissions, which are reverse of the process of the addition of carbocations to alkenes (*16*).

Due to the importance of these alkylation reactions in petroleum industry, the acid-catalyzed alkylations have been extensively reviewed. The HF-amine complexes can be recovered and re-used in alkylations (*21*). Several solid superacidic catalysts such as sulfated Zirconia, Nafion-H, Nafion-silica composites, and heteropoly acids and their salts can also be used in these alkylations, but these catalysts are not industrially applicable due to their fast deactivation (*22*). PVPHF complex containing 22 equivalents of HF to one equivalent of 4-vinylpyridine was shown to be useful for the alkylations (*16*). The addition of polymeric organic bases in relatively small quantities (e.g., HF:amine = 22:1 mol ratio) does not significantly decrease the acidity of HF and is expected to be $\sim H_0 = -10.8$, suitable for alkylation reactions. The RON numbers for the isobutene-isobutylene alkylation reactions using PVPHF complex was found to be 92.9, which is comparable with that obtained using PPHF (HF: pyridine, 22:1) (RON = 91.1), or neat HF (RON = 93.6) (*16*). Not only the used onium poly(hydrogen fluorides) act as Bronsted acid catalysts, but also high dielectric constant medium for the alkylation reactions, which involve free carbocationic intermediates.

Hydrofluorination of Alkenes

Alkenes react rapidly with PPHF at 0-20 °C to give the corresponding fluoroalkanes regioselectively. The electrophilic addition of HF to alkenes

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proceeds in accordance with the Markovnikov's rule. Thus, 2-methylpropene, cyclopentene, cyclohexene, norbornene, cycloheptene react with PPHF at 0 °C to give *tert*-butyl fluoride, cyclopentyl fluoride, cyclohexyl fluoride, 2-norbornyl fluoride, and cycloheptyl fluoride, respectively in 60-90% yields (*23,24*). Typical solvents for these reactions are tetrahydrofuran, or dichloromethane. Other amine-poly(hydrogen fluoride) complexes, such as trimethylamine poly(hydrogen fluoride) may also be used for these transformations. Branched alkenes are more reactive than unbranched alkenes. The absence of rearranged products in the hydrofluorination of cyclohexene shows that free-carbocations are probably not formed in hydrofluorination reactions of alkenes. The regioselectivity in these reactions can be accounted for by the involvement of carbocations in the form of contact or tight ion pairs.

Poly(vinylpyridine)-HF (PVPHF) provides a heterogeneous reagent for these reactions, and the workup procedures are much simplified using this

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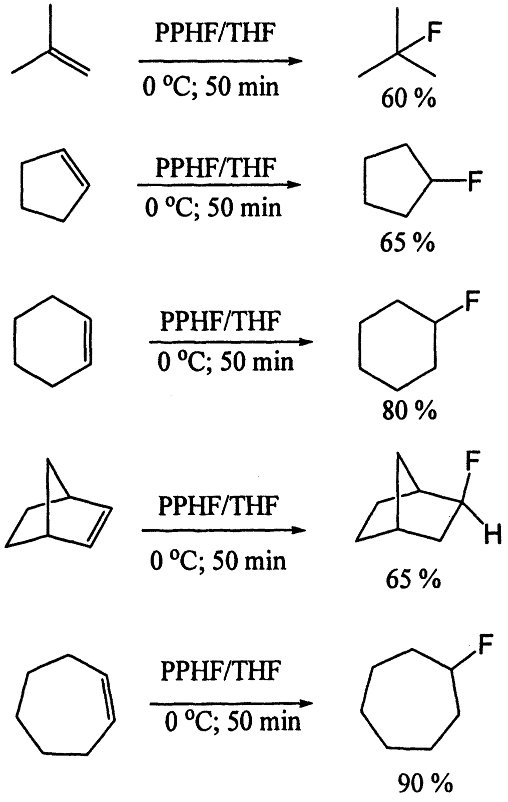
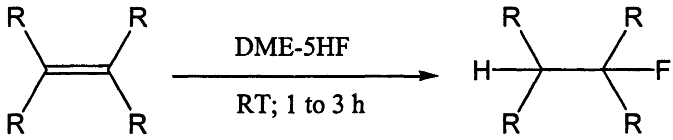
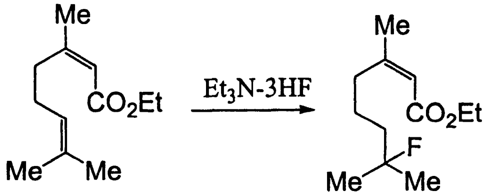


system; i.e., the polymeric reagent is insoluble in the reaction solvents such as dichloromethane and it can easily be separated out by simple filtration. The reaction can be carried out at 0-20 °C. Thus, under these conditions, hydrofluorination of cyclohexene, 1-methylcyclohexene, norbornene give fluorocyclohexane, 1-fluoro-1-methylcyclohexane, and 2-fluoronorbornane, respectively in good yields (*25*).

DME-5HF is also an effective hydrofluorinating agent for a variety of terminal and internal alkenes. For example, 2,3-dimethyl-2-butene, 3-hexene, cycloheptene, 1-hexene, 1-undecene, and 2-norbornene can be hydrofluorinated with DME-5HF at room temperature in 1 to 3 hours to give 73-94% yields of the corresponding fluoroalkanes (*15*).



Triethylamine tris(hydrogen fluoride) is not effective for the hydrofluorination of alkenes, but $Et_3N.5HF$ reacts with alkenes to give the corresponding hydrofluorinated products (*26*). The later reagent is much milder than that of PPHF. Thus, unconjugated dienes can be selectively hydrofluorinated in the presence of conjugated dienes, without the isomerization of the conjugated system.



Hydrofluorination of Alkynes

Alkynes such as 1-hexyne and 3-hexyne react with PPHF regioselectively to give 2,2-difluorohexane and 3,3-difluorohexane, respectively. The orientation

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of the electrophilic addition is in accordance with the Markovnikov's rule (*23*). THF and $CFCl_3$ are commonly used as solvents for these reactions. A variety of internal and terminal alkynes can be dihydrofluorinated at 0 °C to give their corresponding dihydrofluorinated products (*23*). Monohydrofluorination products can be isolated in case of alkynes having electron withdrawing substituents when using tetrabutylammonium bis(hydrogen fluoride). The hydrofluorination of alkynes can also be achieved using PVPHF in trichlorofluoromethane as solvent. For example, 1-hexyne and 3-hexyne gives 2,2-difluoro- and 3,3-difluorohexane, respectively in good yields under these conditions (*25*).

Halofluorination of olefins

Halofluorination of olefins can be achieved by using N-halosuccinimide and PPHF in THF or dichloromethane under mild reaction conditions (e.g., at 0 °C) (*27,28*). Other solvents commonly used are diethyl ether, chloroform, and carbon tetrachloride. These reactions typically proceed under much milder conditions than those of hydrofluorinations. In these reactions, halogen fluoride (e.g, BrF) may be initially formed as transient intermediate reagents. These reactions are in accordance with the Markovnikov's rule: i.e., initial attack of the halogen cations to olefins is regioselective and give the more stable carbocation species, which are trapped by the fluoride anions (generally in a *trans* attack). In addition to N-halosuccinimides, other sources of halogen cations that are commonly used are 1,3-dibromo-5,5-dimethylhydantoin and N-haloacetamides. As sources of fluoride anions, PPHF or triethylamine tris(hydrogen fluoride) are commonly used (*23,29,30*) Polymer supported fluorinating agents such as poly(vinylpyridinium)hydrogen fluoride (PVPHF), and HF complexes of a styrene/vinylpyridine copolymer can also be used for these transformations (*25,31,32*). The halofluorination reactions can also be carried out using 1:1 weight ratio of pyridine/HF (in place of PPHF) as the fluorinating agent *(33)*. In general, the halofluorination reactions are carried out at about -78 °C to prevent olefin polymerizations, and carbocation rearrangements.

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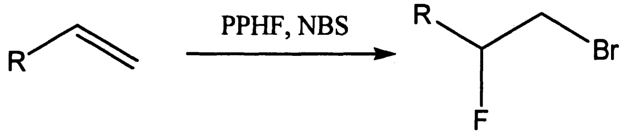
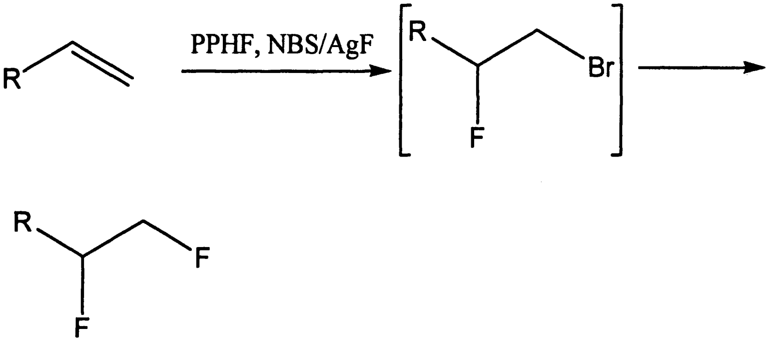
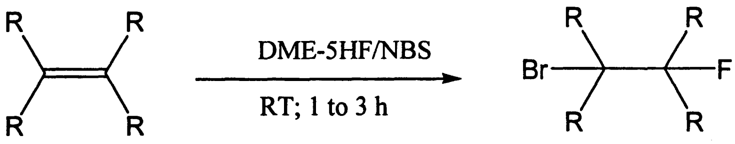
In the presence of AgF/PPHF/NBS, alkenes give vicinal difluorinated compounds through exchange of halide ions *in situ*.





DME-5HF in presence of NBS reacts with a variety of acyclic as well as cyclic alkenes to give the corresponding bromofluorination products in high yields (80-100% for five examples studied) (*15*). The high stability and easy handling of the DMEPHF system makes it a convenient reagent for these transformations. A significant advantage of this process is that during the workup volatile gaseous DME is readily removed from the product mixture.



Fluorination of alcohols

Secondary and tertiary alcohols react at ambient temperatures with PPHF to give the corresponding fluoroalkanes in good yields (*27,34*). Primary alcohols

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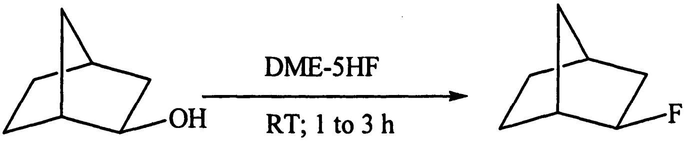
are unreactive under these conditions. However, addition of excess fluoride salts to the reaction medium gives the primary alkyl fluorides. In all of these reactions, addition of chloride or bromide salts give the corresponding chloro- or bormoalkanes.

$$\mathrm{ROH} \xrightarrow[\mathrm{CH_2Cl_2}]{\mathrm{PPHF}} \mathrm{RF}$$

R = secondary
or secondary alkyl

Secondary and tertiary alcohols can also be fluorinated using DME-5HF reagent. The hydrofluorinations using DME-5HF of alcohols such as 1-adamantanol, trityl alcohol, and 2-norbornanol proceed at room temperature in about 3 h to give the corresponding fluorinated hydrocarbons in high yields (*15*). Similarly diethylether-5HF and di-*n*-propylether-5HF complexes also can be used for these transformations (*15*).



85% yield

The low reactivity of primary alcohols to PPHF can be overcome by in situ activation of the hydroxyl group using perfluorobutanesulfonyl chloride (by forming the corresponding sulfonates) in $Et_3N.3HF$ (*35*).

$$\mathrm{ROH} \xrightarrow{\mathrm{C_4F_9SO_2Cl/Et_3N.3HF}} \mathrm{RF}$$

R = primary
or secondary alkyl

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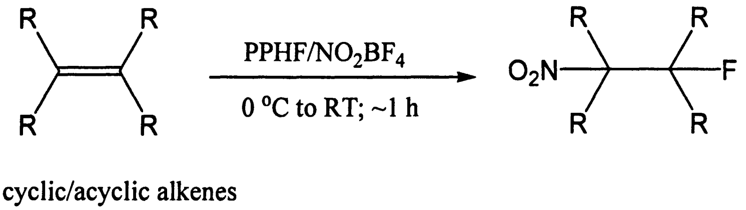
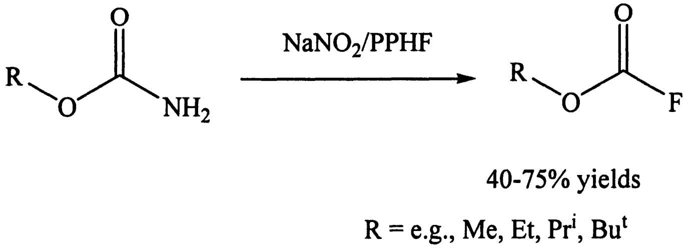
Nitrofluorination of alkenes

Cyclic as well as acyclic alkenes can be nitrofluorinated using PPHF and nitronium tetrafluoroborate (NO_2BF_4) (*27*). Thus reaction of ethene, propene, 2-butene, 1-hexene, chloroethene, 1,1-dichloroethene, and cyclohexene with PPHF/NO_2BF_4 gave the corresponding nitrofluorinated products in 45 to 80% yields. The reaction takes place under mild conditions and accompanying polymerizations are minimized using this reagent combination.



Deaminative fluorination of amino acids and alkyl carbamates

Alkyl carbamates react with PPHF in the presence of an excess of sodium nitrite to give their corresponding fluoroformates in moderate to good yields (*27*). The reaction proceeds through in situ diazotization followed by dediazoniation. This preparation eliminates the necessity of using highly toxic phosgene or their derivatives.



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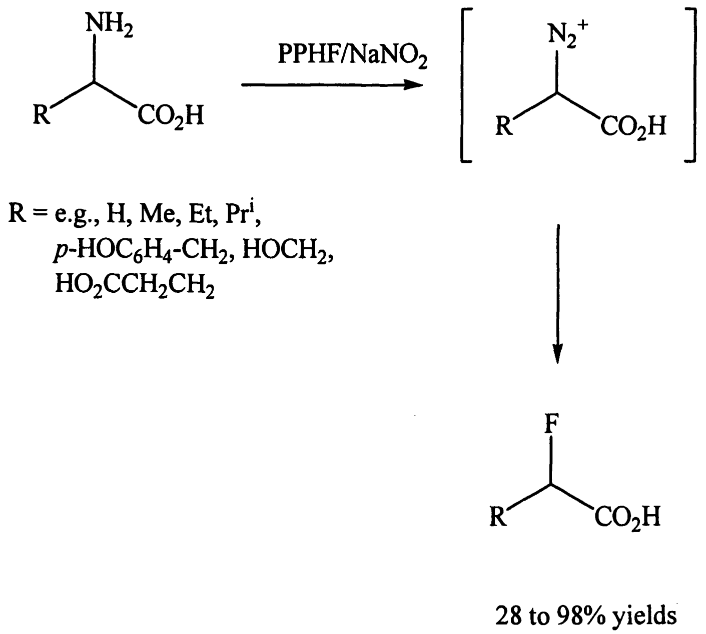
Similarly, in situ diazotization followed by nucleophilic dediazoniation of α-amino acids gives 2-fluorocarboxylic acids in good to moderate yields (*27*). These reactions proceed well even with tyrosine, threonine and glutamic acid which have other functional groups. However, the reaction did not take place with glutamine. In the presence of added sodium halides, the corresponding α-halocarboxylic acids are formed (*29*).



Halofluorination and hydrofluorination of diazoalkanes

Diazoalkanes and diazoketones react with PPHF in presence of added NBS to give their corresponding α-boromo-α-fluoro hydrocarbons (*27*). Reactions in the absence of added NBS proceeds to give the corresponding fluoro ketones or fluoroalkanes. The reaction involves initial electrophilic attack (H^+ or Br^+) on the diazoalkane followed by subsequent nucleophilic fluorinations by F^- species. As α–amino acids can be readily converted to α-diazo esters this method provides convenient method for the preparation of α-amino-α-fluoro acids.

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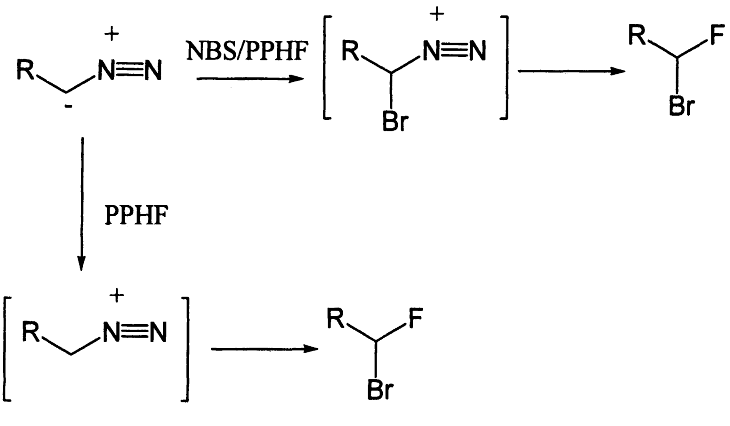

Preparation of acid fluorides from acid chlorides and anhydrides

Acid chlorides and anhydrides can be readily converted to their corresponding acid fluorides using PPHF under relatively mild reaction conditions (e.g., 15 min at room temperature) (*27*).

Deprotection and cleavage of peptides from Merrifield resin

A variety of protecting groups in peptide chemistry such as benzyloxycarbonyl (Z), and *t*-butyloxycarbonyl (Boc) can be cleaved using PPHF. For example, Boc-Asp(OBn)-OH (Bn = $PhCH_2$) reacts with PPHF at room temperature in one hour to give 98% aspartic acid (*36*). Peptides attached to Merrifield resin can be conveniently cleaved by using dimethyl ether-polyhydrogen fluoride (1:15 wt. ratio) complex (*37*). During the cleavage protecting groups such as Boc were also deprotected. However, NH-Fmoc and NH-Ac protecting groups were not affected.

Electrophilic fluorination of diarylacetylenes

Diarylacetylenes can be conveniently transformed into 1,1,2,2-tetrafluoro-1,2-diarylethanes using nitrosonium tetrafluoroborate in PPHF (*38*). Previously these compounds have been synthesized using difficult to handle elemental fluorine or IF/PPHF. The $NOBF_4$/PPHF method of electrophilic fluorination is, however, limited to diarylacetylenes. Dialkylacetylenes acetylenes under these

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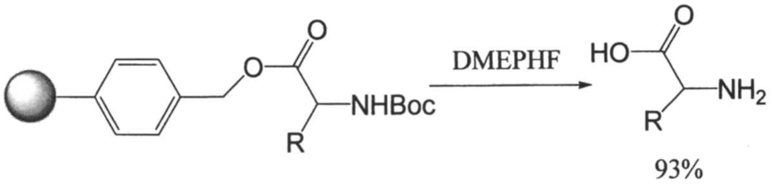
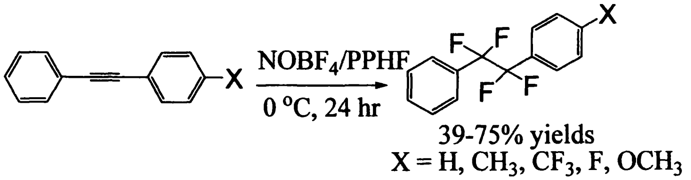
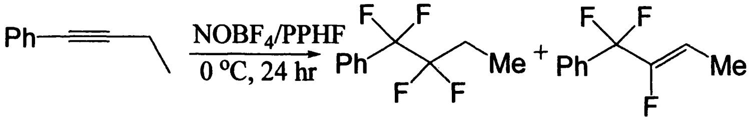


reaction conditions give intractable product mixtures. In the case of arylalkylacetylenes such as 1-phenyl-1-butyne trifluoroalkenes are formed as byproducts due to the competing HF elimination during the reaction.





A possible mechanism for the reaction involves a concerted attack of the electrophilic NO^+ and nucleophilic F^- ions to the alkyne moiety giving 1-fluoro-2-nitrosostilbene, which can undergo conjugate 1,4-addition to give the α,α–difluoroketoxime. The ketoxime undergoes further niotrosative fluorination. The latter intermediate subsequently undergoes nucleophilic displacement by fluoride anion to give the observed 1,2-diaryl-1,1,2,2-tetrafluoroethane and $H_2N_2O_2$, which rapidly decomposes to N_2O and H_2O.

Desulfurative fluorinations

Katzenellenbogen and coworkers have first reported the desulfurative *gem*-difluorinations of 2-alkyl/aryl-substituted-1,3-dithiolanes using 1,3-dibromo-5,5-dimethylhydantoin or N-bromosuccinimide in PPHF.

These reactions proceed through the formation of bromosulfonium ions which undergo nucleophilic fluorination by a S_N2 mechanism.

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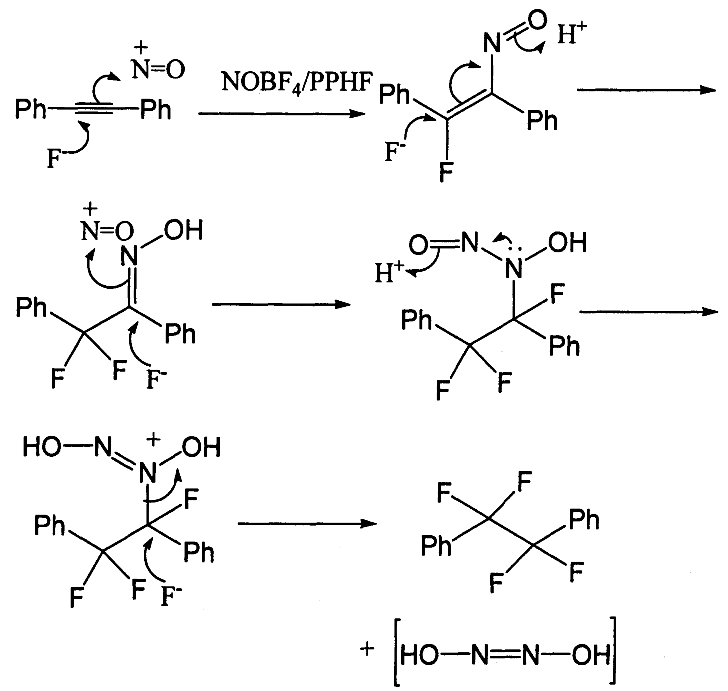

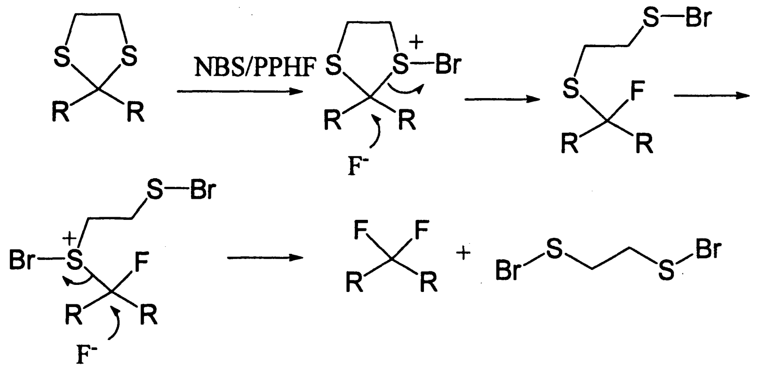

As the electrophilic halogenating agents, NBS has been replaced by SO_2ClF or SO_2Cl_2 for these desulfurative *gem*-difluorination reactions (*39*). Using the latter reagents, workup of the reactions was greatly simplified as the possible byproducts are HCl and SO_2. However, these reactions are limited to diaryl-dithiolanes.

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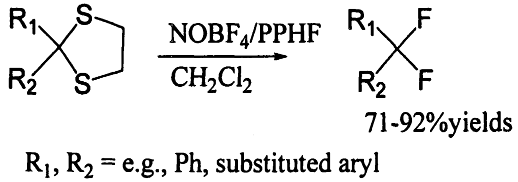
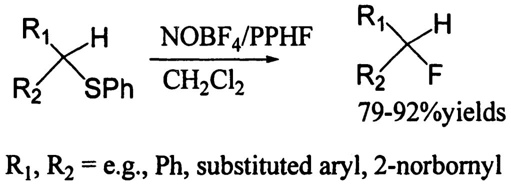
Nitrosonium tetrafluoroborate in combination with PPHF has been found to be an excellent reagent system for desulfurative *gem*-difluorinating agent for dithiolanes (*40*). Phenylsulfides gave monofluorinated compounds under these conditions. The reaction goes through the intermediate formation of the cationic S-nitroso species which undergoes nucleophilic fluorination. Importantly, the aromatic rings are not nitrosated under these reaction conditions.





Dithiolanes have also been transformed to the *gem*-difluoro compounds by reaction with tetrabutylammonium dihydrogen trifluoride (Bu_4N^+ $F(HF)_2$) and N-haloamides such as N-iodosuccinimide and 1,3-dibromo-5,5-dimethylhydantoin(DBH) (*41*). Anodic desulfurization of dithiolanes in $Et_3N.3HF$ also gives the *gem*-difluoro compounds (*42,43*).

2,2-Diaryl-1,3-dithiolanes can be conveniently transformed to *gem*-difluoromethylene compounds using a reagent combination involving Selectfluor^R and PPHF (*44*). The reaction proceeds through the attack of the electrophilic F^+ species on sulfur to give fluorosulfonium ion species as the intermediate, which undergoes nucleophilic fluorination by the fluoride anion. A repetition of the sequence on the resulting compounds gives the *gem*-difluoro compounds. Although the reaction is limited to diaryl dithiolanes, it is a convenient method for the preparation of *gem*-difluoro compounds as it involves mild reaction conditions and easy workup procedures.

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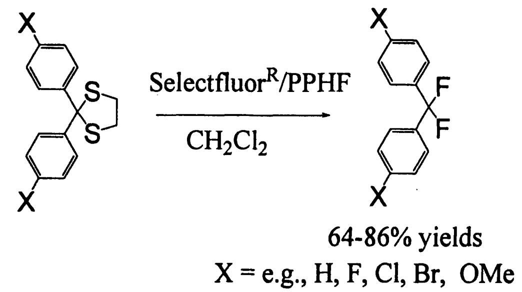
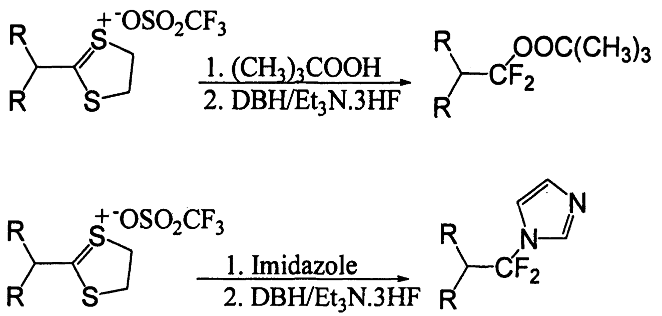


Interestingly, dithianylium salts can be reacted with O- or N- nucleophiles such as alkylhydroperoxides or imidazole and the resulting α-alkoxydithiolanes or α--imidazolyldithiolanes subsequently reacted with $Et_3N.3HF$/DBH to give their corresponding α,α-difluoro ethers or amines (*45*). A variety of compounds such as α,α-difluoroalkyl azides or peroxides also can be prepared using this method.



gem-Difluorination of hydrazones

A variety of hydrazones derived from benzaldehyde, diaryl and arylalkyl ketones react with in situ generated bromine monofluoride (BrF), obtained by the reaction of N-bromosuccinimide (NBS) and PPHF or PVPHF to give the corresponding *gem*-difluoromethylene compounds (*46*). The reaction is limited to compounds that form stable hydrazones, as some of the hydrazones derived from dialkyl ketones readily form azines. The reaction provides a convenient alternative to Rozen's *gem*-difluorination of hydrazones using IF, which in turn has to be prepared *in situ* using elemental I_2 and F_2 (*47*).

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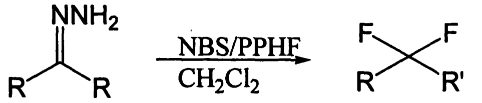
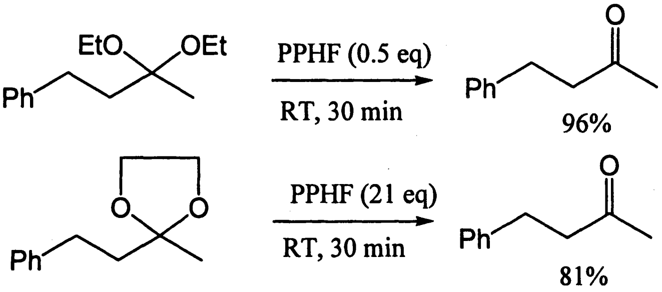


R/R' = e.g., H, Ph; Ph, Ph;
Ph, 4-MeO-Ph; H, $PhCH_2$

Hydrolysis of acetals and ketals

Acetals and ketals can be hydrolyzed using PPHF (0.5 to 20 mol equivalents) in anhydrous acetonitrile followed by aqueous workup. Cyclic as well as acyclic acetals and ketals were hydrolyzed under relatively mild reaction conditions in high yields (*48*).



Oxidative fluorination of phenols

A variety of *p*-substituted phenols can be oxidatively fluorinated at the *ipso*- position using hypervalent iodine (III) reagents in PPHF. Thus diacetoxyiodobenzene and bis(trifluoroacetoxy)iodobenzene react with *para*-substituted phenols such as 4-alkylphenols to give 4-alkyl-4-fluoro-2,5-cyclohexadienones in moderate yields under mild reaction conditions (*49*). Such oxidative ipso-fluorination of binaphthols can be used to prepare atropisomeric cyclohexadienone derivatives (*50*). Nitrogen-substituted polycyclic phenols can be also ipso-fluorinated to give analogous polycyclic cyclohexadienone products (*49*).

The formation of the *ipso*-fluorinated products has been rationalized to proceed through the exchange of the acetoxy group of the hypervalent iodine

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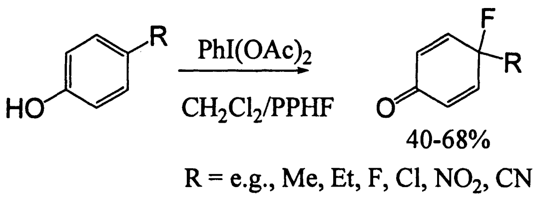
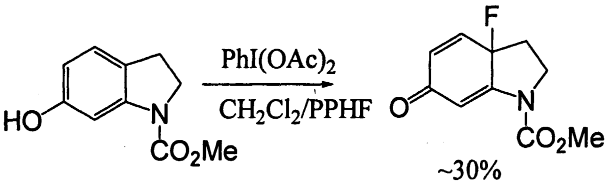
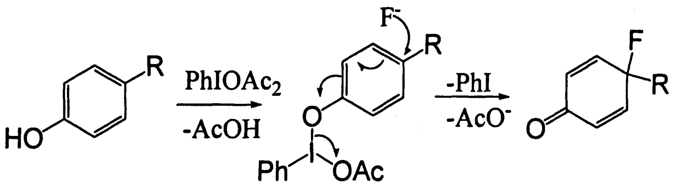
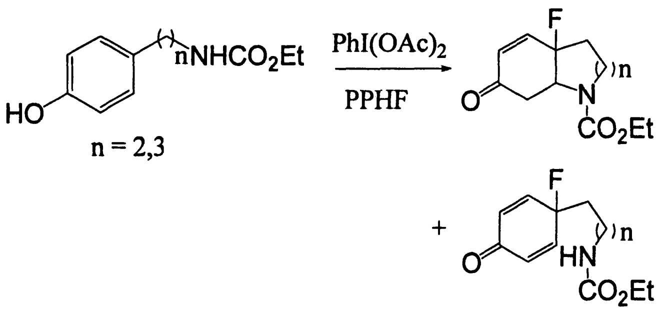




(III) with the phenolic hydroxyl group, followed by 1,4- addition of fluoride ion with concerted departure of iodobenzene and acetate anion.



Oxidative *ipso*-fluorination of phenols can be extended to the preparation of hydroindolenones and hydroquinolenones from the corresponding 4-(aminoalkyl) substituted phenols. The products usually are obtained as a mixture of non-cyclized cyclohexadienones and hydroindolenones or hydroquinolenones (*51*).



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Chapter 5

Diels–Alder and Friedel–Crafts Reactions in Pyridinium-Based Ionic Liquids

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Diels-Alder and Friedel-Crafts reactions have been investigated in pyridinium based ionic liquids (ILs). Various factors such as reaction temperature, reaction time, reactant, catalyst-IL composition, catalyst dosage were studied. The reactions were found to proceed under relatively mild conditions with good overall conversion. The ILs are found to be more effective compared to the organic solvents in enhancing the reaction rate and product yield. Also, the ILs could be recycled and reused efficiently.

Introduction

Recently, ionic liquids (ILs) have gained a lot of attention as green solvents in organic reactions (*1*) and other chemical processes (*2*). The increased interest for their investigations is mainly due to their favorable properties, such as chemical and thermal stability, negligible vapor pressure, non-flammability, high ionic conductivity, high polarity, ease to recycle (*3*). Also they are strongly solvating but non-coordinating; could have profound effect on the activity and selectivity of reactions and in some cases, facilitate the isolation of products. Therefore, ILs are considered as viable substitutes for volatile organic solvents.

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There are literature examples reporting clean synthesis and improved reaction characteristics in ILs. They have been investigated as reaction media in many organic and organometallic syntheses such as hydrogenation (*4*), oxidation (*5*), Diels-Alder reaction (*6*), Heck reactions (*7*), Friedel-Crafts reactions, (*8*) Trost-Tsuji coupling (*9*), esterification (*10*), Beckman rearrangement (*11*). As highly ordered media with environmentally friendly properties, ILs have the potential to influence the outcome of the reactions. All these studies have focused on solvents derived from imidazole. However, pyridinium based ILs also have favorable properties and could be important reaction media for organic transformations. Herein we report our investigation of Diels-Alder and Friedel-Crafts alkylation and alcylation in pyridinium base ILs.

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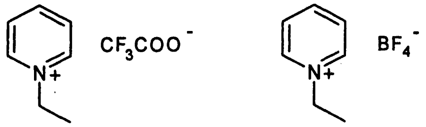
Pyridinium Based Ionic liquids

Two pyridinium based ILs 1-ethyl-pyridinium trifluoroacetate ($[EtPy]^+[CF_3COO]^-$) and 1-ethyl-pyridinium tetrafluoroborate ($[EtPy]^+[BF_4]^-$) were studied. The preparation procedure (*12*) are modified based on the literature methods. (*13*)



$[EtPy]^+[CF_3COO]^-$ $[EtPy]^+[BF_4]^-$

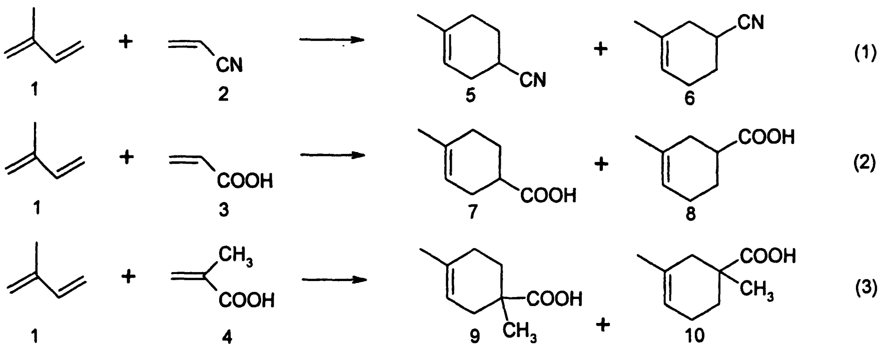
A   B

Scheme 1. Pyridinium based ionic liquids

Diels-Alder Reaction

The Diels-Alder reaction is one of the most important tools for carbon-carbon bond formation. It is a widely used reaction in organic synthesis and in the chemical industry (*14*). The reaction has been investigated using water (*15*), surfactants (*16*), lithium amides (*17*), borane-THF complex (*18*) and imidazolium based ILs (*6*). We investigated the reactions of isoprene **1** with acrylonitrile **2**, acrylic acid **3** and methacrylic acid **4** (Scheme 2) in $[EtPy]^+[BF_4]^-$ and $[EtPy]^+[CF_3COO]^-$ (19).

In a typical reaction, the molar ratio of isoprene: dienophile: IL is 1.5:1:1. All reactions are heterogeneous in nature. The major products are 'para like' (**5, 7, 9**). The results are shown in Table 1.



Scheme 2. Diels-Alder reactions of isoprene with different dienophiles

Table 1. Diels-Alder reactions at 20 °C

Entry	Solvent	Dieno -phile	Time (h)	Yield [a] (%)	Selectivity [b]
1	CH_2Cl_2	2	72	12	64:36
2[c]	Phosphonium tosylates	2	24	38	69:31[d]
3	$[EtPy]^+[BF_4]^-$	2	2 (24)	42 (64)	84:16[d] (66:34)
4	$[EtPy]^+[BF_4]^-$	2	72	83	58:42
5	$[EtPy]^+[CF_3COO]^-$	2	2 (24)	90 (97)	89:11[d] (75:25)
6	$[EtPy]^+[CF_3COO]^-$	2	72	99	75:25
7	CH_2Cl_2	3	72	27	70:30
8[e]	Borane-THF + CH_2Cl_2	3	30	75	-
9	$[EtPy]^+[BF_4]^-$	3	2 (24)	32 (50)	82:18[d] (65:35)
10	$[EtPy]^+[BF_4]^-$	3	72	55	62:38
11	$[EtPy]^+[CF_3COO]^-$	3	2 (24)	97 (98)	95:5[d] (85:15)
12	$[EtPy]^+[CF_3COO]^-$	3	72	98	80:20
13	CH_2Cl_2	4	72	5	58:42
14[f]	Borane-THF + CH_2Cl_2	4	68	66	-
15	$[EtPy]^+[BF_4]^-$	4	24	18	66:34
16	$[EtPy]^+[BF_4]^-$	4	72	22	55:45[d]
17	$[EtPy]^+[CF_3COO]^-$	4	2 (24)	55 (64)	62:38 (54:46)
18	$[EtPy]^+[CF_3COO]^-$	4	72	67	1:1[d]

[a] Determined by GC; [b] "para like": "meta like"; [c] Ref. 20, 80°C; [d] Ratio determined by ^1H NMR; [e] Ref 18, 0°C; [f] Ref. 18.

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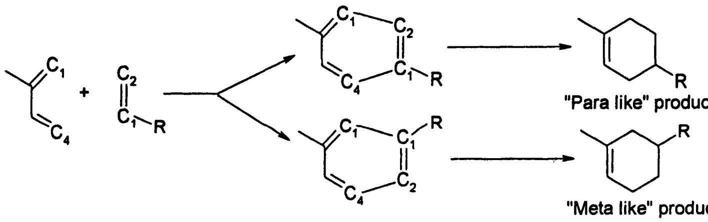
The reaction rate and yields are found to be dependent on the solvent used. The reaction of isoprene with acrylonitrile **2** in CH_2Cl_2 gave very low yield after 72 hours (entry 1). While the same reaction when carried out in $[EtPy]^+[BF_4]^-$ gave 42% yield (entry 3). The reaction seems to slow down there after as we see only 64% in 24 hours and 83% after 72 hours. This reaction also proceeds much faster compared to phosphonium tosylates solvent where even at 80 °C only 38% yield is seen after 24 hours. (ref 23) Reaction in $[EtPy]^+[CF_3COO]^-$ proceeds at a much faster rate resulting in 90% yield in 2 hours. In all cases, however, as the reaction is continued beyond 2 hours there is a decrease in 'para/meta like' product ratio, while overall yield of the combined products increased. Similar results are also seen in reaction of isoprene with acrylic acid **3** (entries 7-12) and methacrylic acid **4** (entries 13-18).

As electron-withdrawing substituents, -COOH and –CN make C-2 more active than C-1 in LUMO of dienophile; whereas electron-releasing substituent, -CH_3 makes C-1 more active than C-4 in HOMO of isoprene. Therefore, the 'para like' products are predominant over 'meta like' products. The varied effect on the rate could be attributed to the difference in coordination of cation and anion in these two solvents (Scheme 1). As Lewis acids, ILs may form complex with the substituent (-COOH or –CN) on dienophiles, which increases the electron-withdrawing capacity of the substituent group, lowers both the energy and orbital of dienophile, thus lowering the reaction activation energy and enhancing both the reactivity and selectivity of the reaction. On the other hand, as high polar solvents, ILs could facilitate the reaction between diene and dienophile, therefore the reaction occurs not only faster but more efficiently than the tranditional organic solvent. In a word, the interaction between dienophile and IL increases the coefficient of C-2 in LUMO of dienophile and make it more efficient to react with C-1 in HOMO of isoprene as shown in Scheme 3.



Scheme 3. The mechanism of Diels-Alder reactions

Due to its electron-donating effect, the methyl group offsets the electron withdrawing effect of the carboxyl group on dienophile, and raises the dienophile orbitals, thus making the methacrylic acid relatively less active than acrylic acid. Therefore, both overall yields and selectivities are lower than those of acrylic acid. With a decrease in temperature to 0 °C, the selectivity increased slightly, and the overall yield can be kept the same by the prolonged reaction

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time. On the other hand at 45 °C the rate of reaction is accelerated, but selectivity to main product dropped significantly to 50~56%. It is also important to note that at 0 °C and 20 °C, the reactions mixtures were in heterogeneous, however increasing the reaction temperature to 45 °C gave a homogeneous mixture.

The reusability of IL was studied by successive runs performed with the recovered $[EtPy]^+[CF_3COO]^-$ for reaction between isoprene and acrylonitrile (Scheme 2, equation 1) at 20 °C for 24 h. The IL could be recovered quantitatively (about 96% yield) and without loss of activity, which is evident from the fact that the overall product yield is not affected even after six runs (92% yield).

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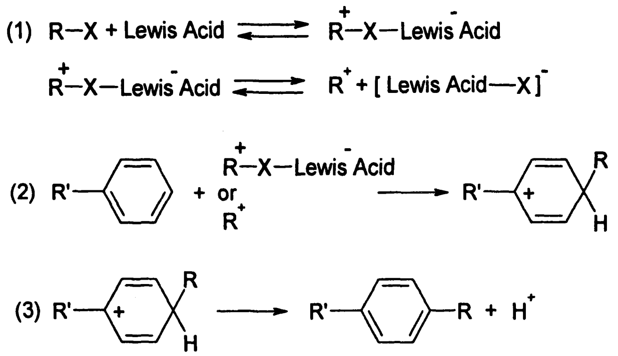
Friedel-Crafts Alkylation and Acylation

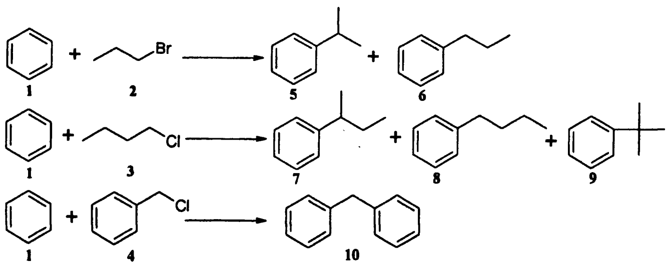
Friedel-Crafts chemistry is important both on laboratory and industrial scale. (21) Traditionally, this reaction can be promoted by Lewis acids, such as BF_3, $ZnCl_2$, $TiCl_4$, SbF_5 etc, though aluminium chloride is mostly used as catalyst. However, it has some disadvantages, such as long reaction time, troublesome product recovery and purification, catalysts can not be reused and formation of environmentally hazardous, corrosive aluminate waste. In contrast, very few examples are reported in the literature where $FeCl_3$, an environmentally favorable catalyst has been used (22). A general mechanism of Friedel-Crafts reaction is shown in Scheme 4 (23). Herein, R- group could be alkyl group for alkyaltion, or carbonyl group for acylation.



Scheme 4. General Mechanism of Alkylation and Acylation

Alkylation

Alkylation of benzene 1 with 2, 3 & 4 is shown in scheme 5 (*24*).



Scheme 5. Friedel-Crafts Alkylation Reactions of Benzene

Both 'iso-' (**5**) and 'n-' product (**6**) were obtained in alkylation of benzene and 1-bromopropane. The reaction proceeds *via* formation of either a carbocation or an acylium ion or a polarized complexes that still contain the leaving group, which is often accompanied by rearrangement of the alkylating group. i.e. The primary propyl cation undergoes a hydride shift to form the more stable isopropyl cation, therefore isoropylbenzene is major product.

Table 2. Friedel-Crafts alkylation of Benzene[a]

Entry	Reactant	Catalyst-Solvent	Conv.(%) rt (50 °C)	Selectivity[b] (%)
1	**2**	$[EtPy]^+[BF_4]^-$	17 (43)	65 (72)
2	**2**	$[EtPy]^+[CF_3COO]^-$	29 (51)	71 (76)
3	**2**	$AlCl_3$-$[EtPy]^+[BF_4]^-$	60 (81)	75 (84)
4	**2**	$AlCl_3$-$[EtPy]^+[CF_3COO]^-$	72 (91)	78 (93)
5	**2**	$FeCl_3$-$[EtPy]^+[BF_4]^-$	56 (80)	74 (81)
6	**2**	$FeCl_3$-$[EtPy]^+[CF_3COO]^-$	71 (90)	77 (89)
7	**3**	$[EtPy]^+[BF_4]^-$	21 (45)	66 (75)
8	**3**	$[EtPy]^+[CF_3COO]^-$	34 (55)	76 (80)
9	**3**	$AlCl_3$-$[EtPy]^+[BF_4]^-$	68 (87)	76 (88)
10	**3**	$AlCl_3$-$[EtPy]^+[CF_3COO]^-$	77 (96)	81 (93)
11	**3**	$FeCl_3$-$[EtPy]^+[BF_4]^-$	67 (88)	74 (87)
12	**3**	$FeCl_3$-$[EtPy]^+[CF_3COO]^-$	77 (94)	83 (94)
13	**4**	$[EtPy]^+[BF_4]^-$	<1 (6)	100 (100)
14	**4**	$[EtPy]^+[CF_3COO]^-$	<1 (12)	100 (100)
15	**4**	$AlCl_3$-$[EtPy]^+[BF_4]^-$	21 (47)	100 (100)
16	**4**	$AlCl_3$-$[EtPy]^+[CF_3COO]^-$	35 (59)	100 (100)
17	**4**	$FeCl_3$-$[EtPy]^+[BF_4]^-$	20 (44)	100 (100)
18	**4**	$FeCl_3$-$[EtPy]^+[CF_3COO]^-$	33 (56)	100 (100)

[a] molar ration of benzene: alkylating reagent: catalyst: IL = 2: 1: 2: 1;
[b] selectivity to major product.

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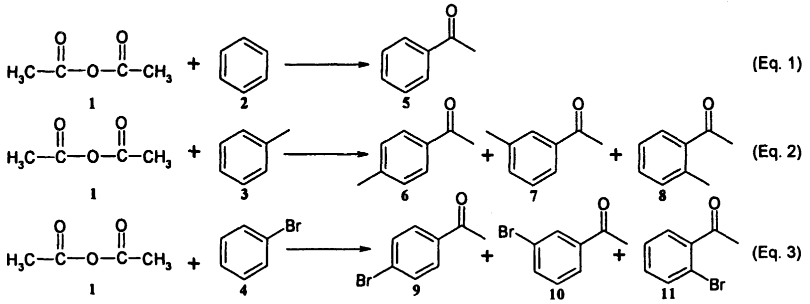
Interestingly, a significant conversion is obtained even with absent of any catalyst entries. (1, 2, 7, 8, 13, 14) A comparison of the results of ILs containing aluminum chloride with iron chloride system shows the same catalytic activity. This indicated that the $FeCl_3$-IL can efficiently replace $AlCl_3$-IL in the Friedel-Crafts Alkylations. Also, a comparative study of two different temperatures (rt and 50 °C) showed that higher product conversion and selectivity are obtained at higher temperature. However, further increasing the temperature to 75 °C resulted in decreased yield and selectivity of the desired product, while unidentified byproducts formed.

In alkylation of benzene with 1-chlorobutane (Scheme 5, equation 2), tert-butylbenzene, thermodynamically most stable of the three, was expected to be the major product. However, interestingly sec-butylbenzene is the major product. Entries 13-18 show the results of alkylation of benzene with benzyl chloride, the product conversion decreased significantly compared to previous cases, which may be due to the steric hinderance effect.

Acylation

The acylation reactions of acetic anhydride **1** with benzene **2**, toluene **3** and bromobenzene **4** have been investigated in pyridinium based ILs (*25*). As shown in Scheme 6 equation 1, acetophenone was obtained as the major product in acylation of benzene **2** with acetic anhydride **1** in different catalyst-IL systems at various temperatures (Table 3).



Scheme 6. Friedel-Crafts acylation reaction with acetic anhydride

The significant amount product formation was seen in IL medium (entry 1, 2), even in the absence of any catalyst. This renders truly green characteristics to the reaction procedure. Further, data show the reaction yields are dependent on the catalyst-solvent chosen. When same reaction was carried out in the presence of a catalyst in IL, the product yields improved. Both $FeCl_3$ and $AlCl_3$ promoted the reaction, giving nearly same yield for the products. This suggests that the $FeCl_3$-IL system could efficiently substitute $AlCl_3$-IL system for the Friedel-Crafts acylations. Also, a comparative study of different temperatures shows that the product conversions were higher when reaction temperature was increased to

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50 °C. However, further increasing the temperature to 75 °C resulted in decreased yield of the desired product, and unidentified byproducts formed.

The acylation of toluene or bromobenzene resulted in three products, i.e. para- (**6/9**), meta- (**7/10**) and ortho-(**8/11**). The major product of this reaction was the para-compound. Results of this reaction in different catalyst-IL systems at room temperature and at 50 °C are summarized in Table 4.

Higher conversions were seen with toluene compared to that with benzene at room temperature (Table 3). This could be due to inductive effect of the CH_3-moiety, which increases the reactivity of the phenyl ring in toluene. However, significant amount of ortho-product is also formed, which results in reduced overall selectivity. Higher product conversions are obtained with increased

Table 3. Friedel-Crafts acylation of acetic anhydride 1 with benzene 2 [a]

Entry	Catalyst-Solvent	Conv.(%) rt / 50 °C / 75 °C	Selectivity (%) [b] rt / 50 °C / 75 °C
1	$[EtPy]^+[BF_4]^-$	51 / 72 / 78	100 / 97 / 69
2	$[EtPy]^+[CF_3COO]^-$	60 / 77 / 81	100 / 99 / 71
3	$AlCl_3$-$[EtPy]^+[BF_4]^-$	77 / 92 / 94	100 / 96 / 70
4	$AlCl_3$-$[EtPy]^+[CF_3COO]^-$	84 / 98 / 99	100 / 99 / 74
5	$FeCl_3$-$[EtPy]^+[BF_4]^-$	73 / 90 / 93	100 / 94 / 73
6	$FeCl_3$-$[EtPy]^+[CF_3COO]^-$	82 / 97 / 97	100 / 97 / 75

[a] molar ration of benzene: acetic anhydride: catalyst: IL = 2: 1: 2: 1;
[b] selectivity to major product.

Table 4. Friedel-Crafts acylation of aromatics

Entry	Aromatics	Catalyst-Solvent	Conv.(%) rt / 50 °C	Selectivity (%)[a] rt / 50 °C
1	3	$[EtPy]^+[BF_4]^-$	55 / 75	57 / 66
2	3	$[EtPy]^+[CF_3COO]^-$	62 / 80	61 / 72
3	3	$AlCl_3$-$[EtPy]^+[BF_4]^-$	77 / 89	63 / 70
4	3	$AlCl_3$-$[EtPy]^+[CF_3COO]^-$	86 / 98	65 / 77
5	3	$FeCl_3$-$[EtPy]^+[BF_4]^-$	74 / 89	63 / 71
6	3	$FeCl_3$-$[EtPy]^+[CF_3COO]^-$	85 / 96	67 / 80
7	4	$[EtPy]^+[BF_4]^-$	54 / 71	61 / 74
8	4	$[EtPy]^+[CF_3COO]^-$	63 / 77	69 / 82
9	4	$AlCl_3$-$[EtPy]^+[BF_4]^-$	76 / 86	73 / 86
10	4	$AlCl_3$-$[EtPy]^+[CF_3COO]^-$	84 / 95	83 / 92
11	4	$FeCl_3$-$[EtPy]^+[BF_4]^-$	73 / 88	76 / 87
12	4	$FeCl_3$-$[EtPy]^+[CF_3COO]^-$	82 / 93	85 / 93

[a] selectivity to major product

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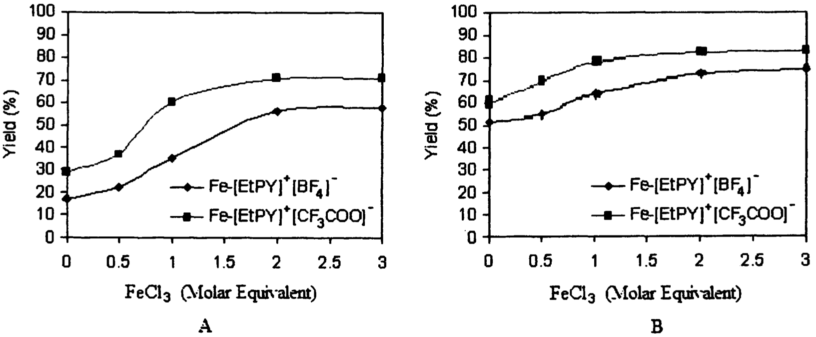
temperature. In entries 7-12, the data suggests that an electron-withdrawing group Br- renders bromobenzene less reactive than benzene and toluene. As a result, the conversion is slightly lower than the previous reactions. However, the selectivity is relatively higher than for toluene. This could be due to ortho- and para- direacting and deactivating effect of Br, seem more predominant on the para- position. Also, in this case, steric effect favors the para-product. Though, improved conversions are seen with the catalyst-IL system, it is noteworthy that reaction could also proceed in IL alone.

Dosage of $FeCl_3$

In order to find a suitable catalyst amount in the $FeCl_3$-IL system, the Friedel-Crafts reactions of benzene with bromopropane A (or with acetic anhydride B) were studied at room temperature for 4 hr (Scheme 7).



Scheme 7. The effect of dosage of $FeCl_3$

As data shows that better results are obtained with increasing the amount of $FeCl_3$ to 2 molar equivalents. However, further increasing the amount of $FeCl_3$ to 3 equivalents did not have any significant change in product yields. It is demonstrated that the optimized $FeCl_3$ amount is 2 equivalent.

Recycling and Reuse of ILs

The reusability and efficiency of ILs were investigated by successive runs performed in the recovered $[EtPy]^+[BF_4]^-$ or $[EtPy]^+[CF_3COO]^-$ at 50 °C for 4hr.

As results in Table 5 shows, both ILs could be recovered quantitatively and almost without loss of activity and selectivity. This is evident from the fact that the conversion of the Friedel-Crafts alkylations is not affected even after the 3rd run. However, yields of ILs recovery from the used catalyst-IL system were relatively low. Also, the conversion dropped dramatically, even product selectivity remained nearly unaffected.

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Table 5. Recycling of ILs in the alkylation of benzene and 1-chlorobutane

#	$[EtPy]^+[BF_4]^-$		$[EtPy]^+[CF_3COO]^-$		$FeCl_3$-$[EtPy]^+[BF_4]^-$		$FeCl_3$-$[EtPy]^+[CF_3COO]^-$	
	Recov. (w%)[a]	Conv. (%)[b]	Recov. (w%)[a]	Conv. (%)[b]	Recov. (w%)[a]	Conv. (%)[b]	Recov. (w%)[a]	Conv. (%)[b]
0	-	45/75	-	55/80	-	88/87	-	94/94
1	94	43/73	93	53/75	88	75/84	90	82/92
2	92	44/74	92	51/78	85	67/83	86	76/90
3	93	41/72	93	50/76	89	65/81	87	75/91

[a] Isolated recovered yield; [b] Conversion/(selectivity to major product).

Table 6 shows both ILs could be recovered quantitatively with negligible loss of activity in acylation reations even after 3rd run. However, , even $FeCl_3$-IL system could be recovered efficiently, the conversion dropped dramatically. After 3rd trial, conversions obtained were nearly same as seen with IL alone. This may be due to lost catalytic activity of the $FeCl_3$-IL system.

Table 6. Recycling of ILs in the acylation of benzene and acetic anhydride

#	$[EtPy]^+[BF_4]^-$		$[EtPy]^+[CF_3COO]^-$		$FeCl_3$-$[EtPy]^+[BF_4]^-$		$FeCl_3$-$[EtPy]^+[CF_3COO]^-$	
	Recov. (w%)[a]	Conv. (%)	Recov. (w%)[a]	Conv. (%)	Recov. (w%)[a]	Conv. (%)	Recov. (w%)[a]	Conv. (%)
0	-	70	-	76	-	85	-	94
1	93	68	96	75	90	80	88	90
2	93	67	94	72	87	75	91	83
3	94	65	95	73	89	73	88	81

[a] Isolated recovered yield.

Mechanism of Friedel-Crafts Reaction

$[EtPy]^+[BF_4]^-$ and $[EtPy]^+[CF_3COO]^-$ are suitable solvents for Friedel-Crafts alkylation and acylation. Based on the classical mechanism of acylation (Scheme 4), we propose the following mechanism in IL-MCl_3 (M = Al or Fe) system (Scheme 8). The alkylating or acylating reagent reacts with Lewis acid to form a more electrophilic C^+, which reacts with nucleophilic aromatic ring resulting in cyclohexadienyl cation. Removal of the proton reforms the aromaticity generating HCl as byproduct. The reaction rate and results are significantly improved in ILs compared to organic solvents. This is due to ionic nature of the IL medium which makes intermediate $[CH_3CO]^+[MCl_4]^-$ relatively more accessible, thus lowering the reaction activation energy without changing the mechanism of the Friedel-Crafts reaction. Furthermore, the product could be

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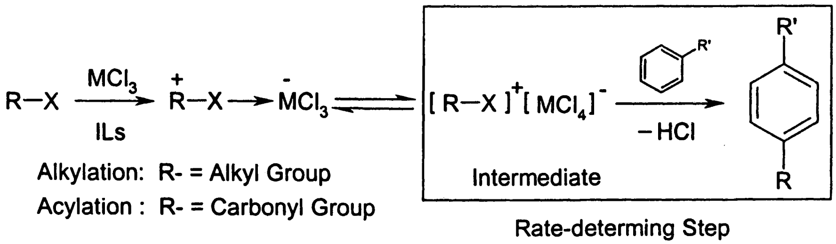
easily extracted with petroleum ether, indicating that the product did not combine with the catalyst, which further renders the reaction "green" characteristics.



Scheme 8. Proposed Mechanism

In all cases, the results with $[EtPy]^+[CF_3COO]^-$ are better than those with $[EtPy]^+[BF_4]^-$, which indicates $[EtPy]^+[CF_3COO]^-$ has relatively more influence on Friedel-Crafts reaction compared to $[EtPy]^+[BF_4]^-$, though they have the same cation. This demonstrates the anions of ILs or the different coordination between cation and anion of ILs are critical for the reactions.

In conclusion, the pyridinium based ILs are suitable media for Diels-Alder reaction and Friedel-Crafts reactions. High conversions were obtained at relatively mild reaction conditions. Combination of $[EtPy]^+[CF_3COO]^-$-$FeCl_3$ is found to be an excellent solvent-catalyst system for Friedel-Crafts reactions, which could efficiently substitute the aluminum catalyst system. Further investigations of application of pyridinium based ILs are underway.

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12. *General Procedure for Synthesis of ILs*: Trifluoroacetic acid or tetrafluoroboric acid (0.2 mol) were slowly added to a stirred slurry of silver (I) oxide (0.1 mol) and distilled water. Then N-ethyl-pyridinium bromide (0.2 mol) was added. The mixture was stirred at room temperature until no more precipitate of silver (I) bromide formed. Silver (I) trifluoroacetate

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may be excess. Therefore, 1M solution of N-ethyl pyridinium bromide was added drop by drop until no more AgBr formed. The mixture was stirred for 10 minutes, and then filtered off the precipitate. Any color and impurities present in the synthesized IL could be removed by passing IL through a charcoal column with distilled water. Finally, the water was removed by rotary evaporation under vacuum. The resulting ILs are dried in an oven overnight at 65 °C.

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24. *General Procedure for Friedel-Cafts Alkylation*: The catalyst, anhydrous $AlCl_3$ or $FeCl_3$ (16 mmol), slowly added to IL (8 mmol), the mixture was stirred at 45 °C until the catalyst completely dissolved. Benzene (16 mmol) and alkyl halides (8 mmol) were directly added to the solution. Two phases

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were formed and the reaction mixture was stirred (250 rpm). After 4 hrs, the mixture was extracted with 3 mL water and 3 mL petroleum ether. Any leftover organics were removed by diethyl ether and the IL was dried at 65 °C under vacuum and then reused. The combined organic extracts were washed with water (3 mL) followed by brine (3 mL). Evaporation of solvent under vacuum gave the product which was purified by FC column and dried over Na_2SO_4.

25. *General Procedure for Friedel-Cafts Acylation*: The catalyst, anhydrous $AlCl_3$ or $FeCl_3$ (16 mmol), slowly added to IL (8 mmol), the mixture was stirred at 45 °C until the catalyst completely dissolved. Acetic anhydride (8 mmol) was added and then aromatics (16 mmol) were added. Two phases were formed and the reaction mixture was stirred at 250 rpm for 4 hours. Then the mixture was extracted by 3 mL water and 3 mL petroleum ether. Any leftover organics were extracted by ethyl ether and the IL was dried at 65 °C under vacuum and then reused. The combined organic extracts were washed with water (3 mL) followed by brine (3 mL). Evaporation under vacuum yielded the product and then purified by FC column and dried over Na_2SO_4.

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Chapter 6

Organic Synthesis in Ionic Liquids Utilizing Organometallic Reagents

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Room temperature ionic liquids (RTILs) have been a focal point of green chemistry and have stimulated interest in both academia and industry for the past several years (1) The physical properties of RTILs offer many advantages. For example, they are non-volatile and thus may be used in high vacuum systems and they are immiscible with a number of organic solvents and thus provide a two phase solvent system. These properties have simplified catalyst recovery in a number of transition metal catalyzed reactions such as Heck reactions (2), ring closing metathesis (RCM) (3), Stille coupling reactions (4), Negishi coupling reaction (5) and Suzuki reactions (6). We have focused our studies on the development of new chemical reactions using these remarkable liquids as solvents in organoboron chemistry.

Reduction of aldehydes using trialkylboranes in ionic liquids

The reduction of aldehydes by organoborane reagents is an important organic transformation. A large number of boron hydrides have been utilized as reducing agents due to their remarkable chemoselectivity (7). However, reductions involving simple trialkylboranes generally require reaction temperatures in excess of 150 °C (8). We have observed that ionic liquids, such as 1-butyl-3-methylimidazolium tetrafluoroborate ($BmimBF_4$), 1-ethyl-3-methylimidazolium tetrafluoroborate ($EmimBF_4$), and 1-ethyl-3-methyl-

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imidazolium hexafluorophosphate ($EmimPF_6$) enhance the rate of trialkylborane reductions (9). For example, tributylborane reduces benzaldehyde at room temperature in $EmimPF_6$ although the reaction can be carried out more rapidly at 100 °C.

Both aromatic and aliphatic aldehydes are reduced by tributylborane in ionic liquids (Table I). The presence of a *para*-substituted electron-donating group appears to hinder the reaction. Only one alkyl group is utilized and thus an equimolar ratio of aldehyde and tributylborane is required. Presumably this is a consequence of the weaker Lewis acidity of the dialkylborinic ester generated after the first reduction step (Scheme 1). The fact that the organic products are readily removed from the ionic liquids *via* distillation or extraction is especially appealing. We repeatedly recycled the ionic solvents and found no decrease in reduction yields.

Table I. Reduction of aldehydes with tributylborane in $EmimPF_6$

Aldehydes	*Time/h*	*Yield(%)*[c]
C_6H_5CHO	16[a]	100
m-BrC_6H_4CHO	16[a]	100
p-FC_6H_4CHO	16[a]	100
o-$CH_3C_6H_4CHO$	16[a]	98
$C_{10}H_{20}O$	48[b]	100
$C_{10}H_{20}O$	24[a]	100
$(CH_3)_3CCHO$	48[b]	100

[a]Reactions carried out at 100 °C. [b]Reactions carried out at rt. [c]NMR yield.

Scheme 1

Allylboration of carbonyl compounds in ionic liquids

Allyboranes react with carbonyl compounds to form homoallylic alcohols, which are important intermediates in the synthesis of natural products and in the pharmaceutical industry. Brown studied the effect of solvent on the allylation of carbonyl compounds and found that poorly coordinating solvents enhance the rate of allylboration reactions (10). Since ionic liquids are poorly coordinating solvents, we examined the use of ionic liquids in allylboration reactions. We found that BmimBr, $BmimBF_4$, $EmimBF_4$ and ethyl ammonium nitrate (EAN) are all effective media for the allylboration of carbonyl compounds (11).

The reactions of a variety of aromatic aldehydes and ketones with allyldiisopropoxyborane were carried out in BmimBr and produced high yields

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of the expected products (Table II). Ferrocene carbaldehyde affords 1-ferrocenyl-1,3-butadiene which is formed via allylation followed by dehydration due to conjugation with ferrocene. 2-Phenylpropionaldehyde produces the *syn* diasteromeric product predominantly. The diastereofacial selectivity is greater than that observed in conventional solvents (12). It is noteworthy that, after extraction of the products, the ionic liquids can be reused. The NMR spectra of the recovered ionic liquid solvents show no evidence of degradation, and little variation in reaction yield is observed using recovered ionic liquids.

The use of potassium alkynyltrifluoroborates in Mannich reactions

The Petasis reaction is a modern variation of the Mannich reaction involving an amine, a carbonyl compound, and an organoborane (13). The method has attracted considerable interest because the three-component process is applicable to a variety of boronic acids, amines, and carbonyl compounds such as α-ketoacids (14), α-hydroxyaldehydes (15) and salicylaldehydes.(16). Examples of the Petasis reaction involving alkenylboronates and arylboronates are well documented but alkynylboron derivatives have not been utilized.

We examined the reaction of potassium alkynyltrifluoroborate salts with formaldehyde and various amines in $BmimBF_4$. Propargylamines are obtained in high yields (Scheme 2). The resultant products are of biological interest because they are selective inhibitors of the rat squalene epoxidase enzyme (17).

In an initial study, the reaction of salicylaldehyde with potassium 1-hexynyltrifluoroborate and dibenzylamine in $BmimBF_4$ produced only 10% of desired product. We then found that the addition of 1 equivalent of benzoic acid increased the reaction yields dramatically. The benzoic acid presumably catalyzes the condensation of the aldehyde with the amine to generate an iminium ion, which then reacts more efficiently with the borate salt (18). The reaction was most efficient in $BmimBF_4$ and DMF; whereas, THF, acetonitrile, 1,4-dioxane, and ionic liquids such as BmimBr and $BmimPF_6$ were less effective.

Reactions of a variety of alkynyltrifluoroborates and carbonyl compounds were then investigated (Table III). Benzaldehyde derivatives lacking an *o*-hydroxy substitutent were found to be unreactive. The reaction is limited to secondary amines, but both aliphatic and aromatic alkynyltrifluoroborates participate. Under the reaction conditions utilized, no heterocycle formation was observed (16).

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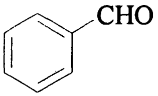
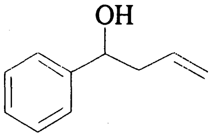
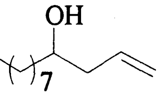
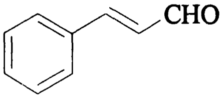
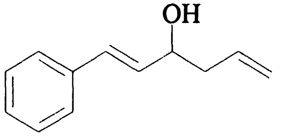
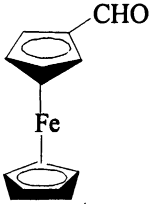
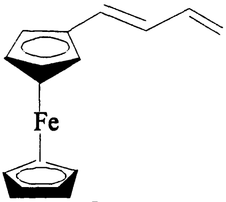
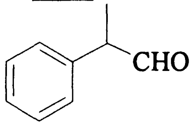
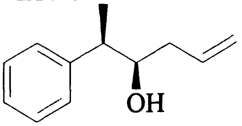
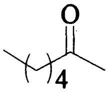
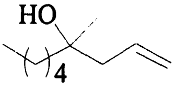
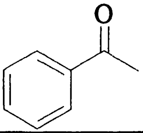
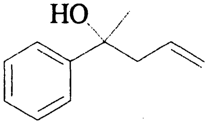
Table II. Reaction of carbonyl compounds with allyl diisopropoxyborane in BmimBr[a]

Carbonyl compound	*Product*	*Isolated Yield*
		87
		86
		84
		82
		85[b]
		82
		83

[a]All reactions carried out at room temperature. [b]*Syn*/*anti* selectivity is 4:1.

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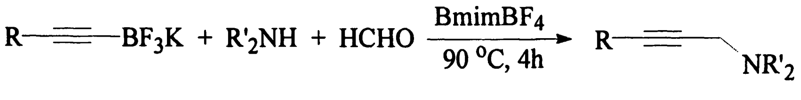
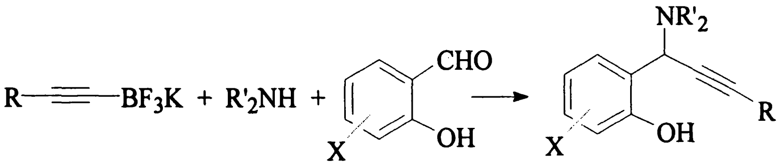


R	Amine	Yield (%)
n-Butyl	Dibenzylamine	92
n-Butyl	Morpholine	90
Phenyl	Piperidine	83

Scheme 2

Table III. Three component condensation of potassium alkynyltrifluoroborates, amines and salicylaldehydes[a]



R[a]	*Amine (2)*	*X*	*Yield %[b]*
n-Butyl	Dibenzylamine	H	81
n-Butyl	Morpholine	3-Me	63
n-Butyl	Morpholine	5-*t*-Bu	76
n-Butyl	Morpholine	5-Cl	53
p-Tolyl	Morpholine	5-NO_2	78
t-Butyl	Morpholine	H	72
1-Cyclohexenyl	Morpholine	H	78
Trimethylsilyl	Morpholine	H	58[c]

[a]Reaction conditions: $BmimBF_4$, 1 equiv. benzoic acid, 80 °C, 20 h.

[b]Isolated yields.

[c]The trimethylsilyl group was removed under the reaction conditions.

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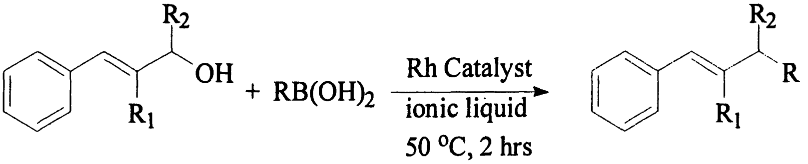
Rhodium-catalyzed cross-coupling of allyl alcohols with aryl- and vinylboronic acids in ionic liquids

Transition-metal-catalyzed allylic alkylation using allyl complexes represents an important carbon-carbon bond forming reaction that is widely used for constructing complex organic molecules. Allylic halides (19), carboxylates (20), carbonates (21), phosphates (22), and related compounds are generally utilized as allylation reagents. On the basis of the viewpoint of atom economy (23), the ability to use allylic alcohols in allylation reactions would be highly beneficial. However, they are rarely used because hydroxide is a poor leaving group. A few approaches have been reported, but they require either severe reaction conditions or unique ligands (24). Coupling reactions of boronic acids with allyl halides (19) and esters (20) are well-known, but the direct coupling of boronic acids with allylic alcohols is highly useful. We investigated the direct allylation of cinnamyl alcohols using boronic acids catalyzed by ligandless rhodium catalysts (Scheme 3) (25).



Scheme 3

Various rhodium catalysts, solvents, and reaction conditions were examined using *p*-tolylboronic acid and cinnamyl alcohol as model substrates. $BmimPF_6$ was found to be the most effective solvent. No reaction was observed in polar solvents such as water and DMF. Common rhodium catalysts were evaluated, and both Rh(I) and Rh(III) were found to be effective. Although bases are commonly used in transition-metal catalyzed coupling reactions, they inhibited this reaction. However, acids increased the reaction rate. The addition of copper salts such as cupric acetate enhanced reaction yields by approximately 10%. The highest yields were obtained using a mixture of $RhCl_3 \cdot xH_2O$ (3 mol %) and $Cu(OAc)_2$ (10 mol %) in $BmimPF_6$ at 50 °C for 2 h. To enhance the utility of the reaction, we examined the reactions of a variety of organoboronic acids (aryl, alkenyl, heteroaryl) and allylic alcohols (Table IV). Electron-rich boronic acids generated higher yields than electron-deficient boronic acids. Steric factors also affected the yield. *Ortho* and *meta* substituted arylboronic acids typically gave lower yields than the *para* substituted arylboronic acids. Sterically hindered alcohols also led to lower yields. Aliphatic alcohols were found to be unreactive. It is noteworthy that the catalyst system can be recycled with no significant loss in reaction yields.

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Table IV. Coupling of organoboronic acids with allylic alcohols.[a]

Boronic acid	*Alcohol*	*Yield (%)*[b]
Phenyl	Cinnamyl	65
p-Methoxyphenyl	Cinnamyl	76
p-Acylphenyl	Cinnamyl	0
trans-β-Styrenyl	Cinnamyl	50
2-Thiophene	Cinnamyl	33
o-Tolyl	Cinnamyl	55
m-Tolyl	Cinnamyl	61
1-Naphthyl	α-Methylcinnamyl	52
p-Tolyl	1,3-Diphenyl-2-propen-1-ol	60
p-Methoxyphenyl	1,3-Diphenyl-2-propen-1-ol	65

[a] Reactions were carried out using $RhCl_3.xH_2O$ (3 mol %) and $Cu(OAc)_2$ (10mol %) in $BmimPF_6$ at 50 °C for 2 hrs. [b]Isolated yields.

Investigation of the behavior of arenediazonium salts with olefins in $BmimPF_6$

Heck reactions of aryl halides in ionic liquids have been studied extensively (1). Since reactions of arenediazonium salts in ionic liquids have not been investigated and diazonium salts have several advantages over aryl halides including the accessibility of precursor anilines and superior reactivity, we investigated reactions of arenediazonium tetrafluoroborate salts with various olefins in $BmimPF_6$ (26).

The reaction of methyl acrylate with phenyldiazonium tetrafluoroborate was investigated first. A variety of ionic liquids were used as solvents and the most effective was found to be $BmimPF_6$. Only traces of product were obtained using either BmimBr or $BmimBF_4$.

After establishing the reaction conditions, a number of arenediazonium salts were examined (Table V). The catalytic system can be recycled at least four times without loss of activity. The reactions of other olefins with diazonium salts were then examined. Methyl acrylonitrile gave satisfactory results but higher temperatures and longer reaction times were required. Vinyl ether and vinyl ester derivatives were unreactive. Surprisingly, when styrene was used as the olefin, the reaction produced the dimerization product, (*E*)-1,3-diphenyl-1-butene, in high yield instead of the expected Heck cross-coupled product.

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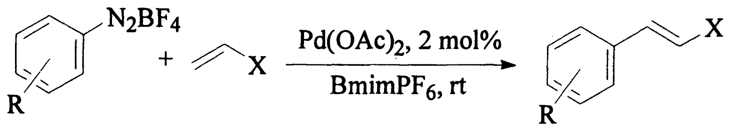
Table V. Pd-catalyzed Heck reaction of arenediazonium salts[a]



R	*X*	*Time (h)*	*Yield (%)*
H	CO_2Me	3	76
p-Br	CO_2Me	3	82
p-Cl	CO_2Me	3	78
p-I	CO_2Me	3	32 (75)[b]
o-CN	CO_2Me	2	80
p-OCH_3	CO_2Me	3	72
p-Cl	CN[a]	4	70[c]
p-OCH_3	CN	4	68[c]

[a]Reaction conditions: methyl acrylate or methyl acetronitrile (1 mmol), arenediazonium salt (1.2 mmol) $Pd(OAc)_2$, (2 mol%) at r.t. or 50 °C, 2–4 h. [b]GC yield in parenthersis, product decomposed on silica gel. [c]Reaction temperature was 50 °C.

At first glance, it would appear that the diazonium salt is not involved in the dimerization reaction. However, in the absence of the diazonium salt, no trace of dimer was detected. We found that 1 mol% of diazonium salt was sufficient to catalyze the dimerization. The reaction was examined using a variety of substituted styrenes (Table VI). No differences in reactivity with respect to the electronic and steric effects of the substituent were observed.Though the role of the diazonium salt in the reaction is still not clear, a free radical mechanism has been ruled out by the fact that no dimerization product formed when AIBN was used in place of the diazonium salt.

Preparation of (*Z*)- and (*E*)-vinyl selenides utilizing vinylboronic acids and vinylboronic esters in ionic liquids

Vinyl selenides have attracted considerable attention in recent years as synthetic precursors. Many selenide preparations involve the use of expensive catalysts or starting materials that are not readily available. Ogawa and his co-workers reported that organic selenols react with acetylenes to generate vinyl selenides (27). However, they were unsuccessful in generating stereochemically pure products, although (*Z*)-isomers formed preferentially.

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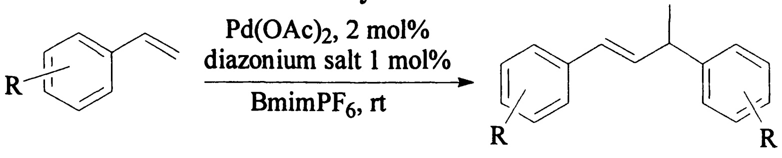
Table VI. Pd-catalyzed, diazonium salt promoted dimerization reactions of styrenes[a]

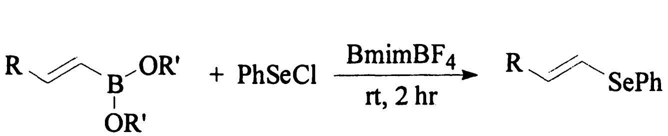


R	*Time (h)*	*Isolated Yield %*
H	1.5	94
p-Cl	1.5	96
o-Cl	2	93
o-Br	2	72
m-Cl	2	89
p-CH_3	1.5	93

[a]Reaction conditions: styrene (1 mmol), $Pd(OAc)_2$ (2 mol %), *p*-nitrophenyldiazonium tetrafluoroborate (1 mol %), r.t., 1.5-2h.

We observed that vinylboronic acids and vinylboronic esters readily react with phenyl selenenyl chloride in ionic liquids such as $BmimBF_4$ and BmimBr to generate the corresponding phenyl vinyl selenides (Scheme 4) (28).

Good yields are obtained in $BmimBF_4$ at room temperature. Several vinylboronic acids and esters were treated with phenyl selenyl chloride. Both (*E*)- and (*Z*)-vinylboronates react (Table VII). Pinacolate esters are also reactive but catechol esters are not suitable substrates due to the electrophilic substitution reactions of the phenyl selenium cation on the catechol moiety (29).



Scheme 4

Conclusion

Ionic liquids are proving to be excellent solvents for carrying out organoborane based organic syntheses. Product separation is straightforward and the solvent systems are readily recycled.

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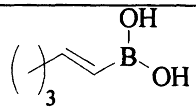
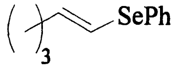
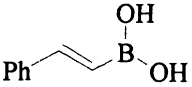
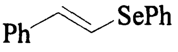
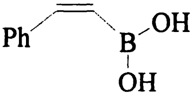
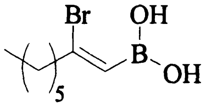
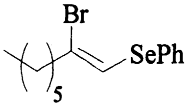
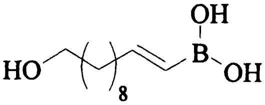
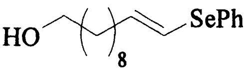
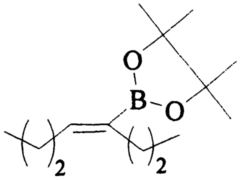
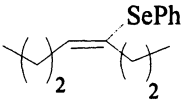
Table VII: Synthesis of vinyl selenides from vinylboronic acids and vinylboronic esters

Alkenyl Boronate	*Product*[a]	*Yield(%)*[b]
		82
		75
		74
		78
		79
		76

[a]All products exhibited satisfactory spectroscopic and analytical data. [b]Isolated

Acknowledgement

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Chapter 7

Transition Metal Complexes in Imidazolium Ionic Liquids as Recoverable and Reusable Homogeneous Catalysts

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Introduction

Ionic liquids can be used as a medium in which perform catalytic reactions and the system recovered and reused in multiple runs (1-6). The necessary condition for this reuse is that the catalyst should remain unaltered in the ionic liquid while the reaction mixture is separated from the ionic melt by precipitation, distillation, extraction or any other physical mean.

The combination of catalysis and ionic liquids derives from the principles of green chemistry that aim to accomplish waste minimization, atom economy and the avoidance of volatile organic solvents (7, 8). Ionic liquids are considered *greener* than conventional organic solvents due to their low vapor pressure, no flammability and the possibility to devise procedures for catalyst reuse. As some other groups (9-18), our work in ionic liquids has been focused on the transformation of successful transition metal catalysts in conventional organic solvents into recoverable and reusable (homogeneous or heterogeneous) catalytic systems.

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In Ionic Liquids in Organic Synthesis; Malhotra, S.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2007.

Efficient catalysts in conventional organic solvents exhibit high activity and selectivity. The target is, without loosing these two features, to develop recoverable and reusable systems based on these successful catalysts. Normally for a given reaction, we have prepared a library of recoverable (either soluble or heterogeneous) systems in order to compare their performance and determine the most efficient catalytic system. In this account we will describe some examples from our own recent work of successful reusable catalytic reactions using transition metal complexes in ionic liquids.

Palladium catalyzed cycloisomerization

One palladium catalyzed C-C bond forming reaction is the formation of a five-member ring by coupling of two terminal C=C double bonds in 1,6-heptadienes as for instance diethyl 2,2-diallylmalonate (Scheme 1) (19-21). This diallylic compound is also one of the substrates of choice to test the activity of ruthenium complexes as catalysts for the ring closure olefin metathesis (22, 23). The difference between the outcome of the palladium and the ruthenium catalysis is that using ruthenium carbenes as catalysts two of the carbon atoms of the substrates are cleaved in the cyclopentene product and the position of the C=C bond is precisely defined. In contrast, in the case of the catalysis by palladium complexes all the carbons of the diallylmalonate are in the product and the position of the C=C double bonds is ill-defined, there being a variable mixture of three isomeric cycloalkenes.

There are not many reactions that can be proposed as test reactions specific for Brönsted or Lewis acids (24, 25). Cycloisomerization of diallylmalonates is one of these test reactions since the activity of the Lewis acid sites increases with their hardness. Conventional Brönsted acids are inefficient to promote cycloisomerization. The main process under Brönsted catalysis is C=C double bond isomerization and eventually ester hydrolysis if water even in trace quantities is present in the medium. Using a consistent series of palladium supported on zeolites as catalysts we have demonstrated that this cycloisomerization is a reaction specific of hard Lewis acids, soft palladium metal complexes being unable to promote the cyclization (25).

The key intermediate in the palladium catalyzed cycloisomerization of diallylmalonates is assumed to be a complex in where palladium is simultaneously coordinated to the two terminal C=C bonds (Scheme 2) (19). The template effect of the palladium atom holding in close proximity the two terminal C=C is a crucial factor leading to the formation of the five member ring.

We have found that 1-butyl-3-methylimidazolium hexafluorophosphate ($bmimPF_6$) is a suitable solvent in which perform the diallylmalonate some

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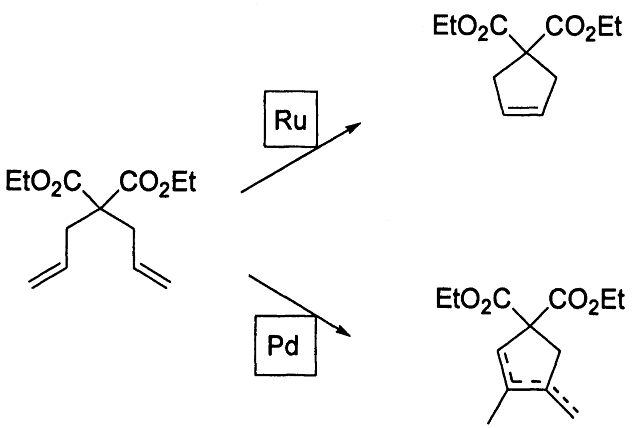
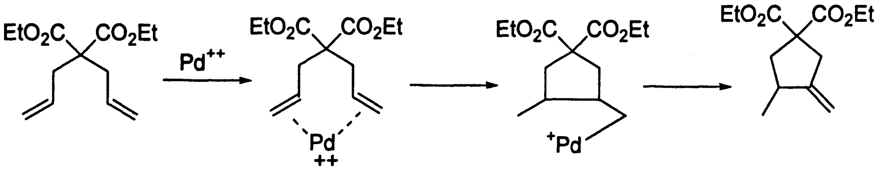


Scheme 1. Differences between ruthenium and palladium catalyzed cyclization of 2,2-diallylmalonates.



Scheme 2. Key intermediates in the reaction mechanism of palladium-catalyzed cycloisomerization of diallylmalonate.

of them such as $PdCl_2$ or $PdBr_2$ have a limited solubility in some of these cyclosiomerization catalyzed by palladium salts and complexes, even though ionic liquids. The catalytic system can be recovered upon extraction of the products with hexane and the ionic liquid reused for five runs with only a minor decrease in the conversion (Table 1).

The conversion and selectivity of the palladium complex dissolved in ionic liquid decrease, however, upon reuse. This is can be easily rationalized as due in part to the loss of palladium during the extraction work-up and to the generation of some Brönsted acid sites in the process. The interconversion of Lewis into Brönsted acid sites is a well known process in those cases in where the Lewis acid is exposed to moisture (25, 26). Since, for the sake of experimental simplicity, the reaction is carried out at the open atmosphere this seems to be the case.

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Table 1. Results of the reuse of $PdCl_2$ in $bmimPF_6$ for the cycloisomerization of 2,2-diallylmalonate to the cyclopentenes shown in Scheme 2.

Use	Conversion	Selectivity
1	100	99
2	100	92
3	100	95
4	97	95
5	77	73

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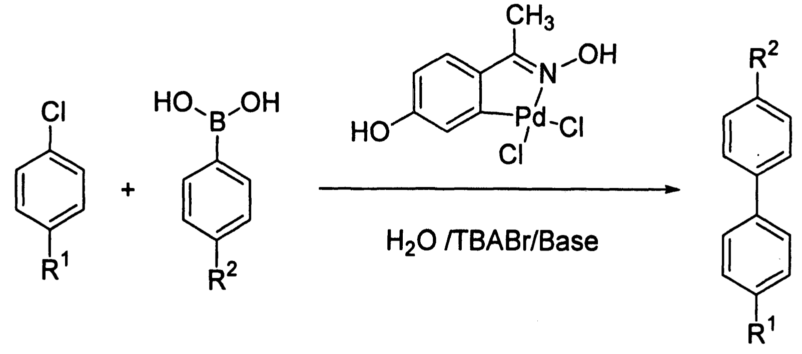
Palladium catalyzed Suzuki-Miyuara and Heck cross-couplings

The report by Nâjera and co-workers that an oxime carbapalladacycle is an active catalyts to promote the Suzuki reaction of chloroaromatics with boronic acid in the presence of a base (Scheme 3) was a significant contribution in the field of palladium catalysed C-C coupling reactions (27, 28). The reaction using this complex can be conducted in water at 100 °C in the presence of a quaternary ammonium salt in those cases in where the chlorinated arene is sufficiently soluble in this solvent.

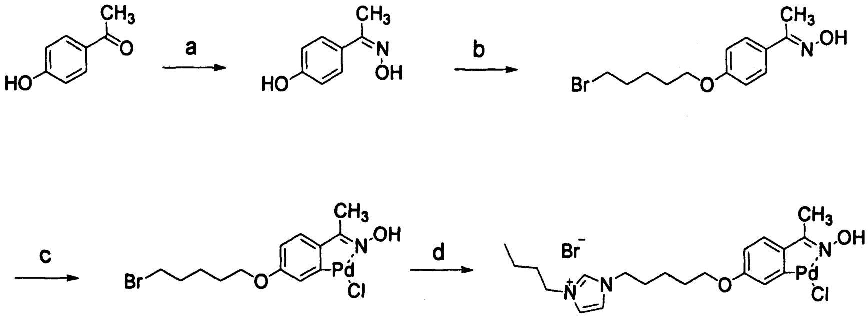
We wanted to convert this highly active oxime carbapalladacyle complex into a reusable catalysts using ionic liquids. In our case, the solubility of the original oxime carbapalladacycle complex in bmim ionic liquids was, however, insatisfactory. To increase the solubility and affinity of the complex we proceeded to the preparation of a derivative in where we introduced a *N*-butylimidazolium tag to make the palladium complex more alike to $bmimPF_6$ as solvent. We have been using the terms *"ionophilic" and "ionophilicity"* to indicate that a substituent has been introduced exclusively to increase the affinity in a given ionic liquids (29). Scheme 4 shows the synthetic route followed to prepare this *ionophilic* oxime carbapalladacycle derivative.

The use of the *ionophilic* oxime carbapallacycle in $bmimPF_6$ as ionic liquid for the Suzuki and Heck cross coupling was, however, disappointing and only low conversions were obtained at long reaction times. We anticipate that this low activity was not due to the intrinsic activity of the ionophilic palladium complex that should be high, but to the depletion of the required base (NaAcO or Na_aCO_3) by reaction with $bmimPF_6$. To test this, we treated $bmimPF_6$ with Na_2CO_3 at the reaction temperature. Acid-base titration after 1 h reaction showed the disappearance of the base. Also ^1H NMR in deuterated methanol show the disappearance of the proton at the 2 position upon reaction with bases through proton to deuterium exchange (30).

In Ionic Liquids in Organic Synthesis; Malhotra, S.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2007.



Scheme 3. Suzuki-Miyaura cross coupling of chlorobenzenes with phenylboronic acid catalyzed by an oxime carbapalladacycle.



a: NH_3OHCl, K_2CO_3; b:1,6-dibromohexane, K_2CO_3; c: $LiPdCl_4$ in CH_3OH, d: N-butylimidazole

Scheme 4. Synthetic route for the preparation of an ionophilic carbapalladacycle complex.

In order to circunvent this problem, that is common to any base-catalyzed reaction in $bmimPF_6$, we proceeded to support the *ionophilic* palladium catalyst on a high surface area aluminosilicate with MCM-41 structure. The aluminum content in the MCM-41 solid mesoporous support was optimized to create in the inorganic oxide a sufficient density of negative charges (one negative charge per each framework Al). Thus, while silicon oxide is neutral, the isomorphic substitution of a Si atom by an Al atom introduces a negative charge in the aluminosilicate that requires the presence of charge balancing cation, the imidazolium moiety in our case. Thus, the imidazolium-substituted palladium complex will remain immobilized on the Al/MCM-41 by Coulomic interactions and a truly heterogeneous solid catalyst was developed.

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As expected, the catalytic activity of the imidazolium-substituted oxime carbapalladacycle adsorbed on MCM-41 for the Suzuki coupling in toluene and DMF as solvent was high for iodides, bromides and even chlorides. Table 2 provides a selection of the results obtained. The solid can be recovered and reused, although analysis of palladium content revealed a depletion of the noble metal indicating that some leaching is taking place during each catalytic reaction.

Table 2. Results of the Suzuki-Miyaura cross-coupling of phenylboronic acid (1.5 equivalents) and *p*-R-C_6H_4-X using the ionophilic carbapalladacycle complex supported on Al/MCM-41.

Run	X	R	Solvent	Con.	Suzuki: Homocoupling
1	I	$COCH_3$	toluene	>99	32:68
2	I	H	toluene	51	51:49
3	I	Br	toluene	75	13:62
4	Br	$COCH_3$	DMF	>99	>99:0
5	Br	H	DMF	57	57:0
6	Cl	$COCH_3$	DMF	87	87:0

Catalytic CO_2 Fixation

There is much current interest in the use of CO_2 as renewable feedstock (31, 32). For this reason, the report that epoxides can react with CO_2 in the presence of transition metal complexes of chromium and cobalt in the presence of bases or nucleophiles (Scheme 5) has been a breakthrough in this area (33-37). The resulting carbonates can be used as octane number enhancers in gasoline formulations.

Our research has been aimed at developing reusable chromium salen complexes (38). We have prepared a series of reusable catalysts for this reaction. Some of these systems are based on the use of bmim ionic liquids and we have tried to study the influence on the catalytic activity of several variables such as: i) the nature of the metal ion in the salen complex, ii) the nature of the charge balancing anion of the imidazolium ionic liquid, iii) the presence of hydrogen or methyl group in the 2 position of the imidazolium ring, iv) the nature of the basic co-catalysts and v) the supercritical conditions of the CO_2.

The activity of homogeneous catalytic systems based on ionic liquids have been compared with that of two solids in where the chromium or aluminium

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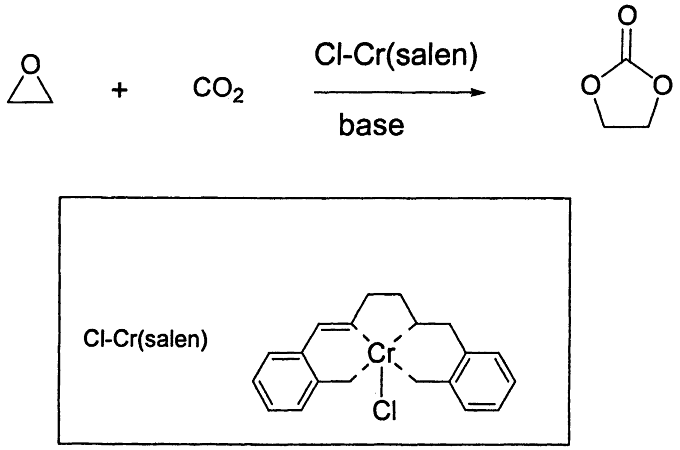

Scheme 5. Chromium(III) salen-catalyzed insertion of CO_2 into epoxides.

salen complex have been attached to a high surface area inorganic oxide such as silica and a novel delaminated ITQ-2 zeolite (39).

We have explored two different possibilities to anchor the metal salen complex to the silicas. In one of them, the silica is modified with 3-aminopropyltrimethoxysilane and the amino-functionalized solid contacted with a solution of metal salen complex in where the apical ligand (normally chloride) has been removed by treatment with $AgClO_4$ (Scheme 6). In this way the metal complex binds to the solid through a coordinative bond at the metal ion. This strategy is synthetically less costly. Moreover, the lability of the coordination bond can allow the complex desorbing under the reaction conditions, thus acting in homogeneous phase. Later, upon cooling the reactor the complex could re-bind into the aminopropyl-modified silica. The problem with this type of ***"boomerang"*** catalysts is that they tend to leach due to the incomplete re-binding to the support and, therefore, the solid becomes eventually depleted of the metal complex.

An alternative methodology consists in attaching covalently the complex to the solid through a linker connecting the support to peripheral positions of the ligand. The problem here is that the preparation of asymmetrically substituted pure salen ligands is synthetically highly demanding. A compromise is reached, preparing in a single step a statistical mixture of three different ligands by reacting simultaneously *trans*-1,2-cyclohexadiamine with two different salicylaldehydes in different proportion. The predominant salicylaldehyde does no have reactive substituents, while the salicylaldehyde in lesser proportion has one reactive chloromethyl substituent adequate to anchor into the functionalized solid. The stoichiometries and the product distribution is indicated in Scheme 7.

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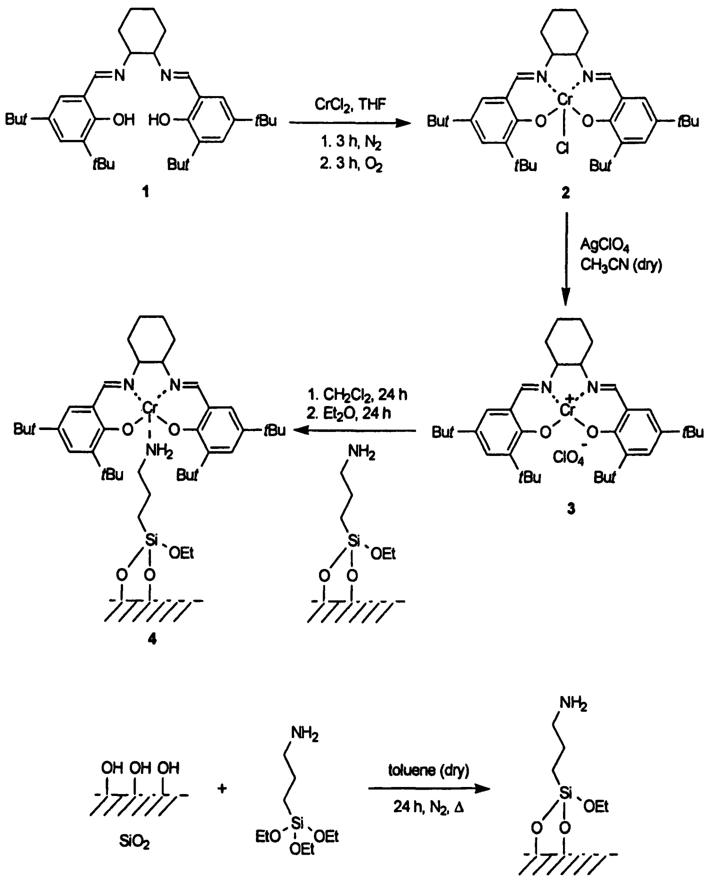

Scheme 6. Procedure for anchoring a chromium(III) salen complex to an aminopropyl-modified silica support.

The activity of some of the catalytic systems studied are summarized in Table 3. The most active and reusable system is that in where the metal salen complex has been covalently attached to amorphous silica. However, the most salient conclusion from Table 3 is that a simple alternative consisting in dissolving commercial (tetra-*tert*-butylsalen)chromium(III) chloride in bmimPF_6 produces a reusable catalytic system whose simplicity and synthetic economy overbalance its somewhat lower activity. It also appears that selectivity towards the cyclic carbonate changes upon reuse of the catalyst dissolved in bmimPF_6. This is again a manifestation of the creation of undesirable Brönsted acid sites producing the epoxide ring opening.

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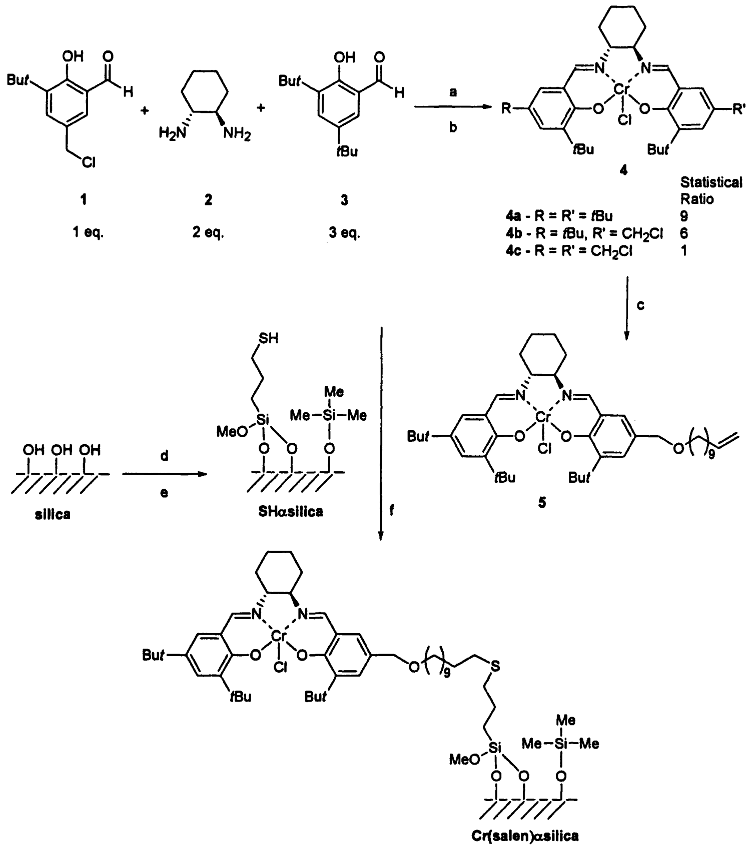

Scheme 7. Synthetic route followed to anchor an asymmetrically substituted chromium(III) salen complex to a silica support. Anchoring has been achieved through the para position of a phenolic moiety of the salen ligand. Note that this procedure does not utilize a pure asymmetrically substituted chromium complex, but a statistical mixture of three.

Conclusions

Dissolving in imidazolium ionic liquids transition metal complexes that are successful catalysts in conventional solvents is a very simple strategy to convert a non-recoverable into a reusable catalytic system. Depending on the nature of the imidazolium and the counter anions, these catalytic systems in imid azolium ionic melts also show promise as medium for enantioselective reactions.

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Table 3. Results of the CO_2 insertion into epoxides to form cyclic carbonates catalyzed by differen chromium(III) salen complexes anchored to solid supports or dissolved in $bmimPF_6$ ionic liquid.

catalyst	Substrate to catalyst molar ratio	Co-solvent	Conversion (%)	Selectivity (%)	Mass Balance (%)
Cr-salen/NH_2SiO_2	875	CH_2Cl_2	66	89	100
Cr-salen/NH_2ITQ-2	816	CH_2Cl_2	71	91	69
Cr-salen∝SiO_2	583	$(MeO)_2CO$	72	100	48
Cr-salen∝SiO_2	583	CH_2Cl_2	74	100	62
Cr-salen∝SiO_2 (use 4)	583	CH_2Cl_2	68	100	48
Cr-salen (not recoverable)	875	CH_2Cl_2	75	100	57
Cr-salen (use 1)	875	$bmimPF_6$	25	79	80
Cr-salen (use 2)	875	$bmimPF_6$	35	68	100
Cr-salen (use 3)	875	$bmimPF_6$	37	67	100
Cr-salen (use 4)	875	$bmimPF_6$	48	56	92
Cr-salen	292	$bmimPF_6$	50	100	54
Cr-salen (not recoverable)	875	CH_2Cl_2	81	93	55

The main problem is, however, the gradual depletion in transition metal complex during reuse as consequence of some degree of complex extraction during product recovery. This depletion can be minimized by modifying the transition metal complex by adding an imidazolium pony tail, thus increasing the *ionophilicity* of the catalyst. This methodology requires further synthetic steps and leads normally to a decrease in the catalytic activity of the transition metal.

Alternative heterogeneous systems in which transition metal complexes are covalently anchored on solid supports are comparatively more costly from the point of view of synthesis and may not show a real advantage over homogeneous catalysis using ionic liquids.

Imidazolium ionic liquids as a medium in where perform catalytic reactions may have limitations when working under basic conditions or using gases as reagents. Bases can react with the hydrogen at the 2 position of the imidazolium ring, thus, becoming neutralized and leading to the reaction of the imidazolium compounds.

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Chapter 8

Approaches to Imino Diels–Alder Reactions in Imidazolium Ionic Liquids

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Abstract: Imino Diels-Alder reactions can be carried out in imidazolium ionic liquids. Depending on the design of the ionic liquid, it may or may not require Lewis acid activation. Several new chiral and achiral imidazolium compounds have been synthesized, but they had melting points above room temperature.

Introduction

The recent interest in ionic liquids and use of ionic liquids in organic reactions is overwhelming (1-7). Our interest in the area grew from the possibility that ionic liquids might improve the Diels-Alder reactions for synthesis (8). We present our work in ionic liquids related to imino Diels-Alder reactions (9, 10). As our entry into this field, we have chosen the imidazolium ionic liquids (Figure 1) (11,12). We have chosen dialkylimidazolium, methylbutyl-imidazolium (MeBuIm) **1** and Dibutylimidazolium (DiBuIm) **2** compounds. For reasons that will be discussed later we considered imidazolium ionic liquids, which have an NH-functional group. Specifically, we chose hydrogenbutylimidazolium (HBuIm) **3** and hydrogenbenzylimidazolium (HBnIm) **4**. For chiral imidazolium ionic liquids, we have chosen (S)-hydrogenmethylbenzyl-imidazolium (HMeBnIm) **5**, (S)-methylmethylbenzylimidazolium (MeMeBnIm) **6**, and (S, S)-dimethyl-benzylimidazolium (DiMeBnIm) **7** ionic compounds were selected.

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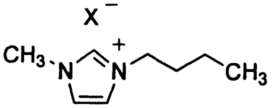
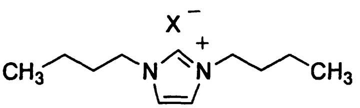
Dialkylimidazolium compound

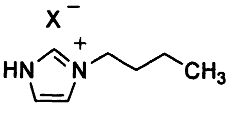


1, MeBuIm

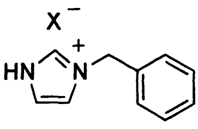


2, DiBuIm

Hydrogenalkylimidazolium compound

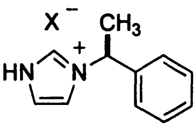


3, HBuIm

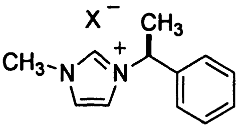


4, HBnIm

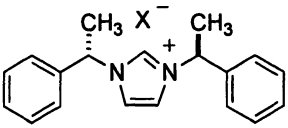
Chiral imidazolium compound



5, HMeBnIm



6, MeMeBnIm



7, DiMeBnIm

Figure 1. Imidazolium compounds of interest.

We examined the simple imino Diels-Alder reactions of Danishefsky's diene **8** (R=Me_3Si) and benzylimine of benzaldehyde **9** (Eq 1). The results are tabulated in Table 1. For a reference point, we attempted the reaction in dioxane, dichloromethane, and ethylacetate to confirm that the cycloaddition did not occur in our hands. However, in dialkylimidazolium salts, the reaction undergoes cycloaddition. The cycloaddition of Danifesky's diene and benzylidinebenzylamine in MeBuIm gave lower yields then in DiBuIm salts (entries 4, 5, 6). Monitoring the reaction by NMR and GC show that there is a significant decomposition of the diene. When the reaction comes to a stop, imine still remains but no diene. To increase the stability of the diene, Danifshesky's diene was replaced with the TBS analog, which gave better yields. Using HBuIm increased the rate of the destruction of the diene and low yields of the cycloadduct were produced (entries 10 and 11). A combination of HBuIm and DiBuIm was attempted to increase the rate of the cycloaddition (entries 12-14). Only a small percentage of HBuIm was needed to affect the rate (entries 10 and 11). Using 10% of HBuIm gave lower yield probably due to the destruction of the diene.

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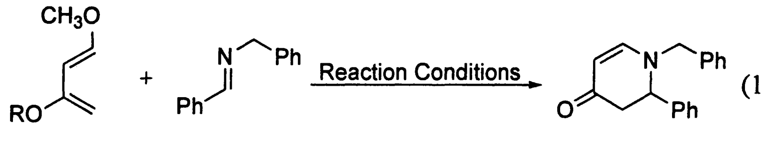

8 9 10

Table 1. Imino Diels-Alder reactions of 8 and 9.

Entry	Reaction Conditions	R[1]	Eq Diene	Conc (M)	Time (h)	Yield (%)
1	Dioxane	TBS	1.4	0.8	12	0
2	CH_2Cl_2	TBS	1.0	1.0	12	0
3	EtOAc	TBS	1.0	1.1	12	0
4	MeBuIm	TMS	1.3	0.3	48	21
5	DiBuIm	TMS	1.8	2.0	37.5	43
6	DiBuIm	TMS	2.9	2.0	21.5	59
7	DiBuIm	TBS	1.0	4.2	18	62
8	DiBuIm	TBS	1.2	2.5	16	65
9	DiBuIm	TBS	1.6	1.9	16	57
10	HBuIm	TMS	1.0	1.0	12	16
11	HBuIm	TMS	1.5	0.3	12	19
12	10% HbuIm/DiBuIm/BF_4	TMS	3.7	2.0	23	47
13	1.5% HbuIm/DiBuIm/BF_4	TMS	1.2	2.0	5	55
14	1.5% HbuIm/DiBuIm/BF_4	TMS	3.4	2.0	23	60

[1] TBS=*t*-butyldimethylsilyl, TMS=trimethylsilyl

To be sure that no trace of tetrafluoroboric acid contaminant was catalyzing the cycloaddition, a solution of DiBuImBF$_4$ in dichloromethane was treated with potassium carbonate, Dowex 66, or both. The resulting ionic liquid still showed product. But unexpectedly, in the presence of one or two equivalents of triethylamine, the cycloaddition did not proceed. This interesting turn of events, led us to investigate this reaction in the presence of basic additives and other counter ions. Table 2 summarizes the results using the TBS diene and benzylidinebenzylamine dienophile.

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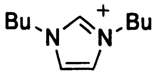
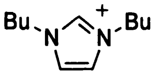
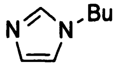
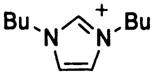
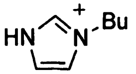
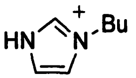
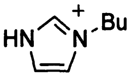
Table 2. Imino Diels Alder reactions.[1]

Entry	Reaction conditions	X^-	Con[2]
1	 pre-treated with K_2CO_3 and/or Dowex 66	BF_4^-	76
2	1 or 2 Eq Et_3N	BF_4^-	0
3	 + 	BF_4^-	0
4		$CF_3CO_2^-$	0
5	 1 Eq Et_3N	BF_4^-	68
6	 1 eq 1-butylimidazole	BF_4^-	50
7		NO_3^-	42

1. For the purpose of these studies, these reactions have not been optimized.
2. Conversion as determined by the ratio of starting material and product by ^1H NMR.

The removal of the Bronsted acid indicates that it is not involved in the cycloaddition (entry 1). Presence of either triethylamine or butylimidazole prevents the reaction (entries 2 and 3). Replacement of the BF_4^- counterion with trifluoroacetate also prevents the cycloaddition. ^1H-NMR of benzaldehyde in DiBuImBF$_4$ shows two distinct aldehyde hydrogen resonances (Figure 2). The minor downfield shift of the aldehyde resonance is typical of Lewis acid coordinated aldehydes. The only potential Lewis acid present is BF_3. The ionic liquid may be facilitating the formation of BF_3 from BF_4^- (Eq 2). The presence of small amounts of fluoride ion may account for the destruction of the silyloxy diene. It's interesting to note that HBuIm can catalyze the reaction in the

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presence of base with counterion BF_4^-, or $CF_3CO_2^-$, or NO_3^-, indicating that N-H can form a strong enough hydrogen bond with the substrate to catalyze the reaction (entries 5, 6, and 7).

$$BF_4^- \longrightarrow BF_3 + F^- \quad (2)$$

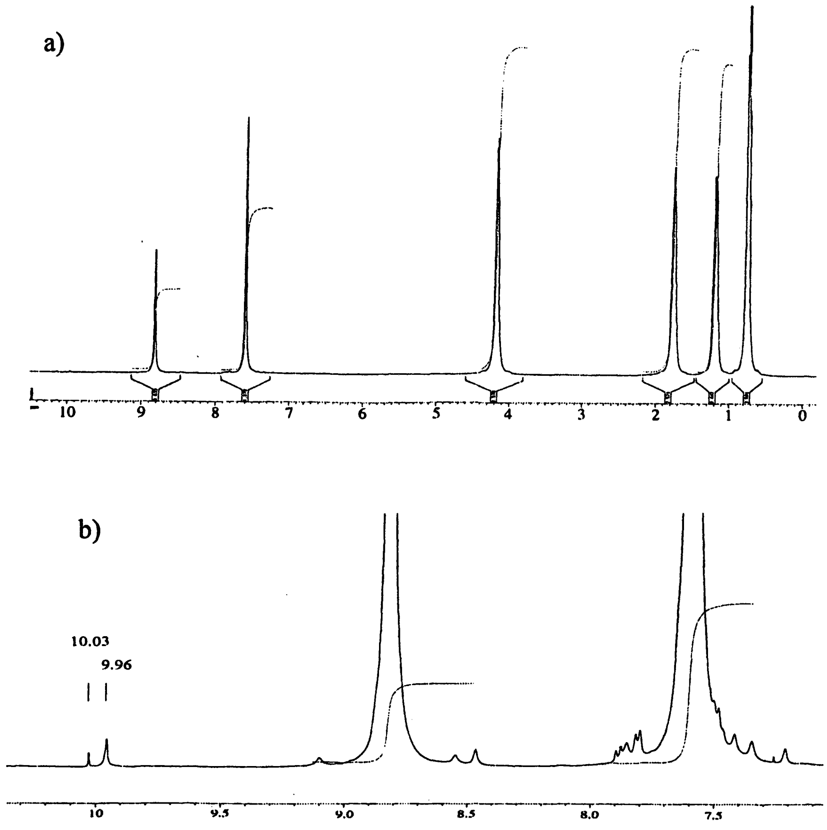

Figure 2. a) ^1H NMR spectra of benzaldehyde in BiBuImBF$_4$. b) Blow up of the aldehyde region.

The fact that dialkylimidazolium needs Lewis acid to catalyze the imino Diels-Alder reactions while the hydrogenalkylimidazolium salts give a more reactive condition confirms our thoughts. It is known that dialkylimidazolium salts can activate carbonyls through hydrogen bonding (Figure 3, complex 11) (13). The HBuIm ionic liquid with the hydrogen bond to the charged nitrogen

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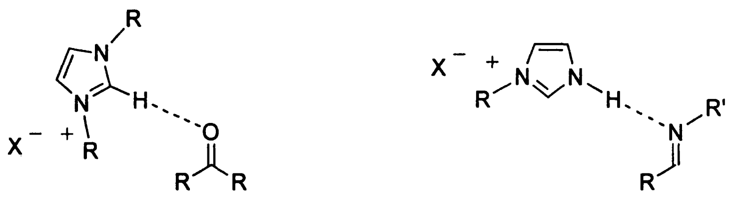


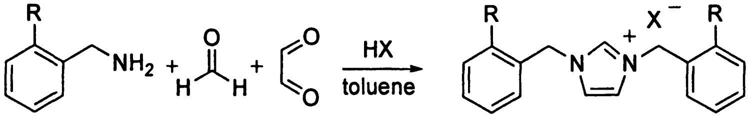
11 **12**

Figure 3. Hydrogen bonding by dialkyl and hydrongenalkyl imidazolium compounds.

should induce a more reactive condition through a stronger hydrogen bond (complex **12**).

We examined the properties of dibenzylimidzolium derivatives. Symmetrical derivatives were synthesized by known methods (Eq 3 and Table 3) (14,15). In all cases, the imidazolium compounds were solids at room temperature.

Dissymmetrical versions were synthesized by similar methods (Figure 4, Table 4). In this case, most were also solids at room temperature (entries 6-10).



(3)

13 **14**

Table 3. Symmetrical dibenzylimidazolium salts.

Entry	R	X⁻	M.p. range(°C)
1	H	BF_4	85-87
2	H	NO_3	64-67
3	H	Camphor Sulfonate	68-72
4	H	CF_3CO_2	71-73
5	OCH_3	BF_4	131-135
6	OCH_3	NO_3	169-170
7	Cl	BF_4	94-96
8	Cl	NO_3	123-129
9	Cl	Camphor Sulfonate	156-160

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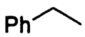
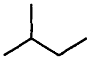
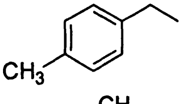
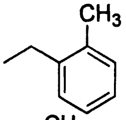
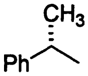
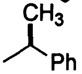
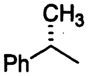
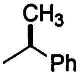
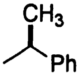
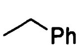
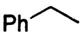
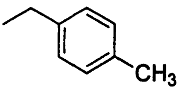
Table 4. Melting points of desymmetrical imidazolium salts.

Entry	R^1	R^2	X^-	M.p. range
1			BF_4	liquid[1]
2			BF_4	solid/liquid[1]
3			BF_4	viscous oil
4			CF_3CO_2	glass
5	H		BF_4	liquid
6	H		BF_4	85-90
7	H		CF_3CO_2	94-95
8	H		NO_3	89-91
9	H		Cl	132-134
10	H	Bu	CF_3CO_2	42-45
11	H	Bu	NO_3	liquid
12			BF_4	64-67

[1] Mixture of symmetrical and dissymmetrical imidazolium compounds.

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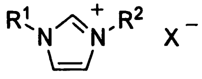
In Ionic Liquids in Organic Synthesis; Malhotra, S.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2007.

Imidazolium salts derived from optically active (S)-benzylmethylamine were viscous oils when the counterion was tetrafluoroborate and a glass for trifluororacetate anion. The hydrogen-(S)-benzylmethyl-imidazolium with tetrafluoroborate was a liquid at room temperature. In the case of entries 1 and 2, mixtures of dissymmetrical imidazolium salts formed resulting in liquid mixtures that were not separated. Compound $HBuNO_3$ was a liquid at room temperature.



15

Figure 4. Dissymmetrical imidazolium compounds.

In summary, imino Diels-Alder cycloadditions can be carried out in imidazolium ionic liquids. For dialkylimidazolium salts, Lewis acids are needed; and in the case of BF_4^- counter anion, BF_3 seem to be generated in situ. Most of the dibenzylimidazolium salts synthesized were found to be solids. Some of these salts with BF_4^- counterion that were liquids and glass, however, these compounds may lead to the formation of BF_3. $HBuImNO_3$ was also found to be a liquid capable of carrying out imino Diels-Alder reactions.

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Chapter 9

Synthesis of Homoallyl Ethers via Allylation of Acetals and Aldehydes in Ionic Liquids

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The TMS triflate catalyzed allylation of acetals to yield homoallyl ethers proceeds smoothly at room temperature in ionic liquids. A one-pot method for the conversion of aldehydes to homoallyl ethers in an ionic liquid has also been developed. This methodology is attractive because it allows allylations to be carried out at room temperature. Ionic liquids offer a convenient replacement for CH_2Cl_2, the commonly used solvent for such reactions.

Introduction

Room temperature ionic liquids are becoming increasingly popular as solvents in organic synthesis for several reasons (*1, 2*). They are practically non-volatile and hence do not pose the risks associated with volatile organic compounds. In addition, they are non-flammable and can be recycled easily without any significant loss in activity. Often, unexpected or improved reactivity is seen in ionic liquids. Although ionic liquids have several attractive features, they do have some drawbacks. Ionic liquids are very expensive and often,

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reactions carried out in ionic liquids still require the use of generous amounts of organic solvents for product isolation. Further, their toxicity by contact and environmental fate is not very well known. Hence, ionic liquids are attractive alternatives to organic solvents only when their use promotes new reaction pathways or allows for milder reaction conditions than would be otherwise possible. In addition, product isolation must be facile and should avoid the use of organic solvents when possible. In this study, we demonstrate the use of ionic liquids as attractive solvents for the synthesis of homoallyl ethers from acetals and aldehydes under relatively mild conditions.

Of all the organic reactions, carbon-carbon bond forming reactions rank among the most important. Of particular interest are Lewis acid catalyzed carbon-carbon bond forming reactions since there is a wide range of selectivity and catalytic behavior among various Lewis acids. The allylation of acetals using organosilicon reagents has attracted much attention as a useful method to generate homoallyl ethers. Several catalysts have been used to effect this transformation. These include $TiCl_4$ (*3*), $AlCl_3$ (*4*), $BF_3{\cdot}Et_2O$ (*4*), trityl perchlorate (5), diphenylboryl triflate (*5*), montmorillonite (*6*), Pb/Al (*7*), trimethylsilyl bis(fluorosulfonyl)imide (*8*), $(CH_3)_3SiI$ (*9*), TMSOTf (*10*), $TiCp_2(CF_3SO_3)_2$ (*11*), CF_3COOH (*12*), $BiBr_3$ (*13*), trimethylsilyl bis(trifluoromethanesulfonyl)amide [$TMSNTf_2$] (*14*), $Sc(OTf)_3$ (*15*), indium metal (*16*), and $Bi(OTf)_3{\cdot}4H_2O$ (*17*). While most of these allylations require an activated alkene such as allyltrimethylsilane, other allyl group sources such as allyl bromide (*4*), and lithium *n*-butyltriallylborate (*18*) have also been used. Most of these methods require the use of chlorinated organic solvents such as CH_2Cl_2 and often inconveniently low temperatures. With increasing environmental concerns, it is imperative that new "environment friendly" solvents be developed and used. In order to develop mild procedures for the synthesis of homoallyl ethers, we considered the use of ionic liquids as solvents.

In an earlier study (*19*) we reported that trimethylsilyl triflate (TMSOTf) smoothly catalyzes the addition of allyltrimethylsilane to acetals at room temperature in the ionic liquids, butylmethylimidazolium hexafluorophosphate, [bmim][PF_6], **1** and butylmethylimidazolium triflate, [bmim][OTf], **2** (Scheme 1).

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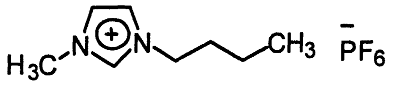
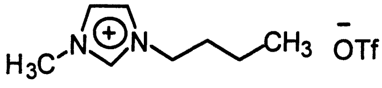
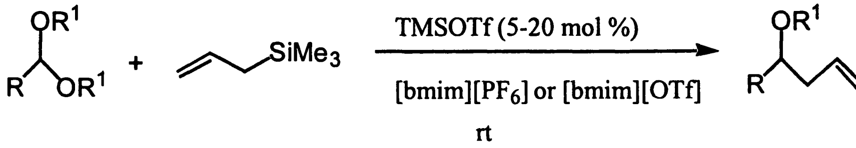


1



2

The reaction progress was followed by TLC. Some of the acetals were not completely soluble in the ionic liquids, and hence it was important to stir the reaction mixture well. If the ionic liquid was used alone (no added TMSOTf), no allylation was observed. If the observed catalysis were due to any trace halide impurities in the ionic liquids, one would expect the allylation to proceed in the absence of TMSOTf.



Scheme 1

The product is isolated by extraction with small amounts of ether, and the ionic liquid can be re-used after drying at 70 °C under vacuum. This procedure works well at room temperature and avoids the use of chlorinated solvents such as CH_2Cl_2 that are typically used for allylation of acetals. The results are summarized in Table 1. In the case of cinnamaldehyde dimethyl acetal (entry 5), it was especially important to insure that the ionic liquid was dry (*20*). Otherwise, considerable amounts (20-50 %) of cinnamaldehyde formed during the course of the reaction. It has been reported that with $TiCl_4$ as the activator, the reaction of cinnamaldehyde dimethyl acetal with allyltrimethylsilane gives only the diallylated product (*4*). Even at low temperatures (-78 °C) the monoallylated product was not formed. Similar results were obtained when allylation of cinnamaldehyde dimethylacetal was carried out using allyl bromide in the presence of $AlBr_3$ (*7*). In contrast, we did not observe any diallylated product using TMSOTf as the catalyst in [bmim][PF_6] or [bmim][OTf] and the monoallylated product was obtained in good yield in both the ionic liquids. No diallylation product was observed when the allylation was carried out using TMSOTf in CH_2Cl_2 as the solvent (*8*). When the allylation of cinnamaldehyde dimethyl acetal was attempted neat, the results were not reproducible and in most trials, an exothermic reaction occurred leading to the formation of black tar. The chemoselective allylation of 2,2′-diethoxyacetophenone **3** in [bmim][OTf] proceeded smoothly to afford the corresponding homoallyl ether **4** (Scheme 2). Thus the acetal moiety can be selectively allylated over the carbonyl group.

When the same reaction was carried out in CH_2Cl_2, the allylation was very slow and less than 40% product resulting from allylation of the acetal formed after 24 h. With 5 mol% $Bi(OTf)_3{\cdot}4H_2O$ as the catalyst in CH_2Cl_2, no reaction was observed (*17*). This example illustrates that ionic liquids are not a mere substitute for volatile organics—rather, they can significantly influence the

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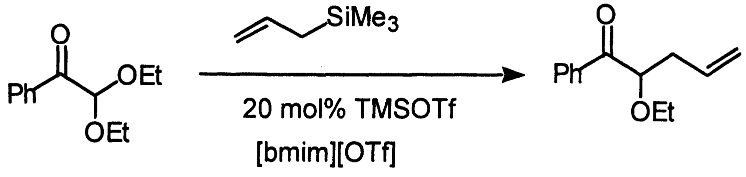

3 4

Scheme 2

outcome of the reaction. In Table 2, yields of allylation of three acetals using three different methods are compared. It can be seen that allylations using TMSOTf or $TiCl_4$ in CH_2Cl_2 require inconveniently low temperatures while allylations in ionic liquids can be carried out at room temperature.

One drawback of using acetals for the synthesis of homoallyl ethers is that many acetals are not commercially available and hence they need to be synthesized from the corresponding aldehydes. In addition, many acetals are sensitive to moisture and hence have poor shelf lives. Hence we were interested in developing a one-pot synthesis of homoallyl ethers from aldehydes *(21)*. In a related study, we have demonstrated the utility of bismuth triflate, $Bi(OTf)_3{\cdot}xH_2O$ ($1 < x < 4$) as a catalyst for the one pot synthesis of homoallyl ethers from aldehydes (*22*). In this study, the acetal was generated from the aldehyde and then treated with allyltrimethylsilane. The formation of the acetal was monitored by gas chromatography and it was found that even if acetal formation was only 70% complete, the addition of allyltrimethylsilane resulted in complete conversion of the aldehyde to the homoallyl ether. This observation suggested that the addition of the silane pushes the aldehyde-acetal equilibrium to the acetal, which then reacts rapidly with the allyltrimethylsilane. This observation coupled with the fact that TMSOTf in an ionic liquid does not catalyze the addition of allyltrimethylsilane to benzaldehyde prompted us to investigate a one-pot, three-component synthesis of homoallyl ethers from aldehydes (Scheme 3). These results are summarized in Table 3 *(23)*. Since the number of trialkylorthoformates commercially available is limited, we also investigated the use of alkoxytrimethylsilanes to carry out the one-pot synthesis of homoallyl ethers from aldehydes. This allows a wider range of homoallyl ethers to be synthesized

The conversion of aldehydes to homoallyl ethers in the ionic liquid, [bmim][OTf] was extremely rapid (under 5 minutes). The aldehydes are soluble in the ionic liquid but the crude reaction product is not and hence the product separates as a layer as the reaction progresses. Besides the expected homoallyl ether, the crude product was found to contain unreacted allyltrimethylsilane and trialkylorthoformate. Although no ionic liquid could be detected (by ^1H NMR analysis) in the crude product, the recovered ionic liquid did contain up to 20%

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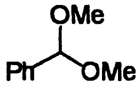
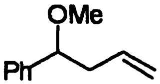
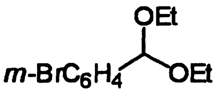
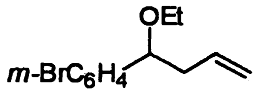
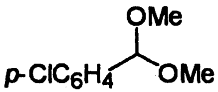
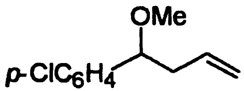
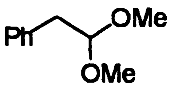
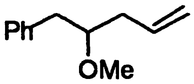
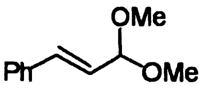
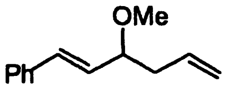
Table 1. TMS triflate catalyzes allylation of acetals in [Bmim][PF_6][a] and [bmim][OTf][a]

entry	*substrate*	*product*	*time & yield (%)[b] [bmim][PF_6]*	*time & Yield (%)[b] [bmim][OTf]*
1			1 h 68	—
2			1 h 15 min 80	1 h 15 min 84
3			1 h 20 min 76	50 min 79
4			1.5 h 76	—
5			5.5 h 81	2 h 15 min 78

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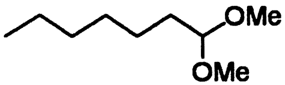
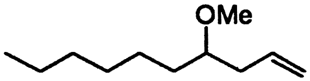
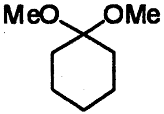
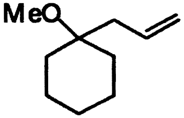
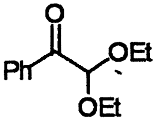
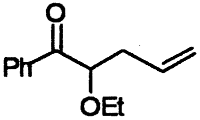
6			25 min 79	45 min 79
7			45 min 62	45 min 74
8			—	23 h 78

[a] Ionic liquids were purchased from Acros chemicals
[b] Refers to yield of isolated and purified product.

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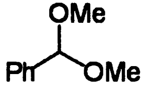
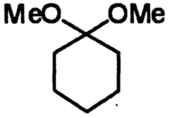
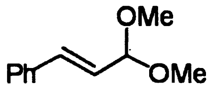
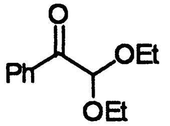
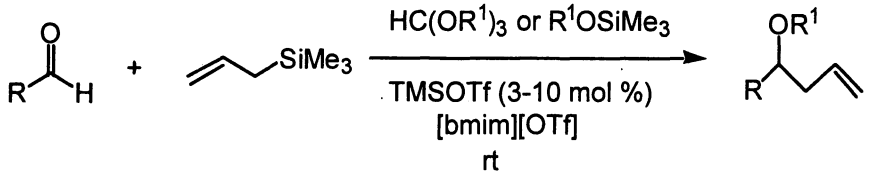
Table 2. Allylation of acetals using allyltrimethylsilane in various solvents

Acetal	% yield[a] using 1 eq $TiCl_4$, CH_2Cl_2, -78 °C	% yield[b] using 1-10 mol % TMSOTf, CH_2Cl_2, -78 °C	% yield using 20 mol % TMSOTf, [bmim][OTf], rt	% yield[c] using 1 mol % Bi $(OTf)_3$, CH_2Cl_2, rt
	74 (GC yield)	88 (GC)	68[d] (isolated)	84 (isolated)
	71 (GC yield)	81 (isolated)	74 (isolated)	82 (isolated)
	diallylation 100 (GC yield)	monoallylation 78 (isolated)	78 (isolated)	84 (isolated)
	–	40 % conversion	78 (isolated)	NR

[a]Data from reference 3 and 4.
[b]Data from reference 10.
[c]Data from reference17.



Scheme 3

of the homoallyl ether product. In order to achieve complete separation, the ionic liquid was extracted with diethyl ether (3 x 5 ml). The recovered ionic liquid was found to be effective in catalyzing subsequent reactions although with each run, the reaction took longer unless 1-2 mol% TMSOTf was added. The results with aliphatic aldehydes were less promising and required the use of 10 mol% catalyst. A moderate yield of the expected homoallyl ether product was obtained from 3-phenylpropionaldehyde.

In summary, the use of ionic liquids as useful solvents for the allylation of acetals as well as for the direct conversion of aldehydes to the corresponding homoallyl ethers has been demonstrated. The reactions are catalyzed by TMS triflate and can be carried out at room temperature.

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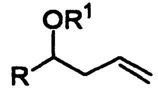
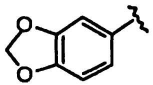
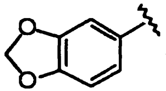
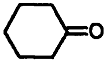
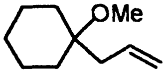
Table 3. One-Pot Method for Conversion of Aldehydes to Homoallyl ethers in [bmim][OTf][a, b]

entry	Substrate RCHO R =	% TMSOTf	Reagent	Product 	Time & Yield (%)[b]
1a	Ph	5	$HC(OMe)_3$	R =Ph, R^1 = Me	10 min, 78
1b	*p*-$CH_3C_6H_4$—	5	$HC(OMe)_3$	R = *p*-$CH^3C^6H^4$— R^1= Me	30 min, 88
1c	*p*-ClC_6H_4—	5	$HC(OMe)_3$	R = *p*-ClC_6H_4— R^1 = Me	25 min, 82
1d		3	$HC(OMe)_3$	R =  R^1 = Me	5 min, 77
1e	$PhCH_2CH_2$—	10	$HC(OMe)_3$	R = $PhCH_2CH_2$— R^1 = Me	2 h, 48
1f		5	$HC(OMe)_3$		1 h 20 min, 44

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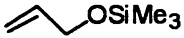
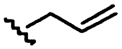
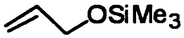
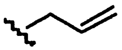
2a[c]	*p*-$CH_3C_6H_4$—	3	$MeOSiMe_3$	R = *p*-$CH_3C_6H_4$— R^1 = Me	10 min, 74
3	*m*-$C_6H_4C_6H_4$—	6	$EtOSiMe_3$	R = *m*-$C_6H_4C_6H_4$— R^1 = Et	10 min, 97
4a[d]	Ph	3		R = Ph R^1 = 	5 min, 81 5 min, 83
4b[d]	*p*-ClC_6H_4—	3		R = *p*-ClC_6H_4 R^1 = 	

[a] Ionic liquid was purchased from Acros Organics. Two equivalents each of trialkylorthoformate and allyltrimethylsilane were used, unless otherwise mentioned.
[b] Refers to yield of isolated and purified product.
[c] Reaction was carried out using 1.2 equivalents of $MeOSiMe_3$ and 1.2 equivalents of allyltrimethylsilane.
[d] Reaction was carried out using 1.2 equivalents of allyloxytrimethylsilane and 1.2 equivalents of allyltrimethylsilane.

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followed by GC. After 25 min, the reaction mixture was extracted with ether (3 x 5 mL). The combined ether extracts were stirred with solid Na_2CO_3 (0.3 g) for 5 min, filtered and concentrated on a rotary evaporator to yield the crude product (1.1331 g) as a clear, yellow oil. The crude product was purified by column chromatography on silica gel (20 g) using 5% ethyl acetate/95% hexane (v/v) as the eluent to yield the homoallyl ether (0.6039 g, 78%, > 98% pure by ^1H NMR, ^{13}C NMR and GC). The recovered ionic liquid (1.92 mL) was dried by heating at 70 °C in an oil bath and re-used.

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Chapter 10

Room Temperature Ionic Liquids as Homogeneous Supports for Synthesis

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In the search for new, more stable homogeneous supports, we have investigated the use of room temperature ionic liquids (RTILs) based on fructose. These RTIL supports have been employed both in the support of reactants and reagents. They greatly facilitate product/by-product separation as well as enable recycling of the support. Key features that have been noted include the ability to tune the solubility/miscibility properties of the support to aid in separation and recycling and the potentially limited utility of these supports in situations that involve basic conditions.

In the ongoing struggle to make organic synthesis less time-consuming and more efficient, one idea has been to anchor, or support, small molecules on some other surface. This basic concept has proven to be very useful and is the heart of modern heterogeneous supported synthesis. More recently, the idea of homogeneous supported synthesis has been introduced. In this case, the goal is to combine the benefits of conventional homogeneous synthesis (good mass transfer and reaction rates, wide range of reaction types and conditions) with the benefits of heterogeneous solid supported synthesis (ease of separation). There have been a number of approaches to this concept, with the polyethyleneglycol (PEG) tethers of Janda being the most popular (Figure 1) (1). By now, a wide range of catalysts, reagents, and reactants have been tethered to these types of supports and, since they are homogeneous in many conventional solvents, used

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in much the same fashion as their conventional "solution-phase" counterparts. At the end of the reaction, however, dilution of the reaction with a solvent (typically methanol or water) then results in the prepitation of the tethered material, thereby enabling the facile separation via filtration that is characteristic of heterogeneous supports.

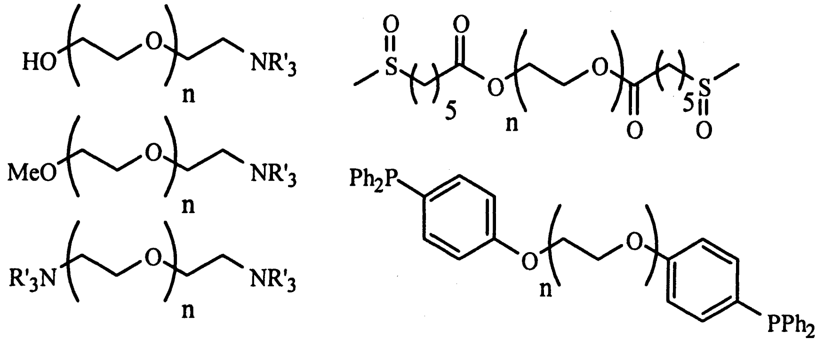

Figure 1. Examples of homogeneous supports and supported reagents.

Although clearly advantageous, there are some issues that remain to be solved with these homogeneous supports. First, they are very high molecular weight in comparison to the materials that are being supported, resulting in very low loading values (2). The simplest PEG tags have molecular weights in excess of 2000 just to support a single molecule. Higher loadings can be achieved using more exotic and expensive dendrimeric PEG-type supports, but these materials are not always amenable to use in syntheses where "intermolecular" reactions can occur between different reaction centers on the same dendrimer (3). This problem is particularly vexing in peptide synthesis (4). Another problem with PEG-based materials is their limited chemical stability to oxidative, free radical, or strongly acidic conditions. Further, the metal-chelating properties of PEG renders these supports incompatible with a variety of the metal-mediated reactions that are the main-stays of organic synthesis.

In the search for new homogeneous supports, an attractive option is room temperature ionic liquids (RTILs). Ordinarily, these materials are viewed as recyclable solvents for organic and inorganic synthesis (5). At the same time, they are increasingly finding applications in other areas as well, including battery applications, chromatographic stationary phases, and separation science. Viewed as supports, RTILs have a number of potential advantages. First, they are relatively low molecular weight compared to long PEGs, thereby leading to higher effective loadings. Second, they exhibit good chemical stability and compatibility with a wide range of organic reaction conditions. Third, their

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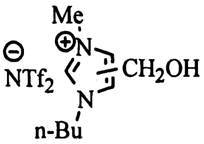
physical properties (such as miscibility/solubility, viscosity, and density) can be tuned by variations in the anionic and cationic components.

The most obvious challenge with using RTILs as supports is the method of attachment of the compound to be supported to the RTIL. In this respect, our recently developed fructose-derived RTIL **1** appeared to be ideal (Figure 2) (6). This material can serve as a reaction medium much like conventional imidazole-derived RTILs, but at the same time the hydroxymethylene moiety provides a site for functionalization of the RTIL. Since there are two main options for types of materials to support - supported reactants and supported catalysts - these will be dealt with separately in the following two sections.



1

Figure 2. Fructose-derived ionic liquid 1

Supported Reactants

Starting with our fructose-derived RTIL **1**, in theory any of a number of reactants could be attached via either an ester or an ether linkage. Our efforts focused on the preparation of supported acrylate **2** (7,8). This acrylate could then be further functionalized in a variety of fashions, including as a dienophile for Diels-Alder reactions.

The synthesis of acrylate **2** appeared to be very straightforward. In practice, though, attempts using standard pyridine or triethylamine mediated conditions afforded a dark, tarry mixture from which only modest amounts of the desired acrylate could be separated. A report by Aggarwal did shed some light as to the potential problem, since he had noted that the use of imidazolium-based ionic liquids as the solvent for the Baylis-Hillman reaction resulted in extensive deprotonation of the C2-position of the imidazolium ring, thereby greatly complicating the resulting reaction mixture (9).

Further support for such deprotonation was noted from the ^1H NMR of the crude acylation mixture, which showed the presence of 2-substituted imidazoles. As a result, an attempt was made to acylate alcohol **1** in the absence of base (Figure 3). Under neat reaction conditions, acrylate **2** was obtained along with hydrogen chloride addition product **3** in a 3:1 ratio. Further optimization lead to the discovery that acrylate **2** could be cleanly prepared by acylation at low

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temperature (-20 °C) in the presence of triethylamine without the concomitant formation of any of product 3.

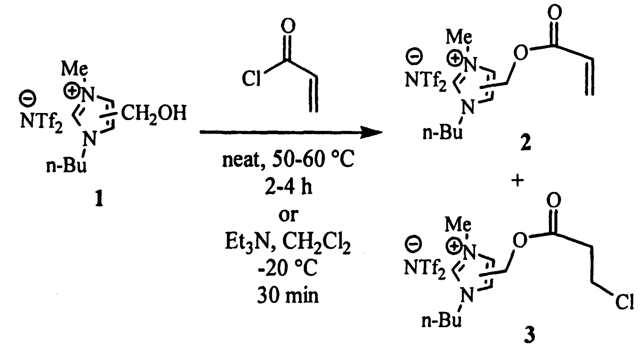

Figure 3. Acylation Conditions.

At this point, acrylate **2** was used in a range of Diels-Alder reactions (Table 1). In all cases, standard thermal conditions were employed. For cyclopentadiene, a solution of the acrylate and the diene was heated to reflux in toluene until starting material was consumed by TLC. For the other dienes, the reaction was performed neat in the presence of hydroquinone to avoid extensive oligomerization of the diene. The Diels-Alder products **4** could be readily isolated by removal of the volatiles *in vacuo*.

The final step in this short sequence was cleavage of the Diels-Alder adducts from the ionic liquid support. Initial attempts focused on simple basic saponification of the ester linkage. Although the carboxylic acid products could be obtained in reasonable overall yield (60-74%), recovery of the ionic liquid support was not as straightforward. The recovered material was a dark brown, viscous liquid that was impure by ^{1}H NMR. Again, we suspected that the basic conditions were deprotonating the C2 position of the imidazolium core and leading to a variety of side reactions. This was supported by the observation that basic transesterification with sodium methoxide in methanol also resulted in a dark brown, viscous liquid.

In an effort to avoid this problem, attention was turned to milder methods for cleaving the Diels-Alder product from the ionic liquid support. After exploring a few sets of conditions, the one that proved to be most effective was a cyanide-mediated transesterification (10). Using a catalytic amount of potassium cyanide in methanol, the methyl esters **5** were obtained in generally good overall yield (Table 1, entries 1-5). More importantly, the ionic liquid support could be recovered in greater than 90% yield. After some experimentation, it was determined that this recovery could be best accomplished by taking up the

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residual mixture of potassium cyanide and ionic support **1** in 4-N sodium hydroxide, followed by extraction with methylene chloride and ethyl acetate. Addition of basic alumina to remove coloration, followed by filtration and removal of the volatile solvents then afforded nearly colorless ionic support **1**. This support was pure and free of solvent and/or Diels-Alder adducts as determined by ^{1}H NMR.

This transesterification method for cleavage from the support has one additional interesting feature - the ability to prepare a number of different esters from the same supported carboxylate. This attribute was briefly examined by treatment of cyclopentadiene Diels-Alder adduct **4** with potassium cyanide and either ethanol or benzyl alcohol (Table 1, entries 6 and 7). In both cases, the anticipated ester products were obtained in good yield and the ionic support **1** could be recovered in nearly quantitative yield.

Finally, the fact that the ionic support **1** can be recovered so readily means that it can be recycled and used in further applications of supported synthesis. The efficiency of this recycling can be seen from the >90% recovery of the ionic support in both the first and second use (Table 1, entries 2 and 3). Further the isolated yield of the final ester product is very similar between the two runs, indicating that the support remains intact.

In an effort to address the base sensitivity of these supports, a 2-methyl substituted version (support **6**) was prepared from fructose in a manner quite similar to that of RTIL **1**, but employing the acetaldehyde/ammonia trimer in the first step in place of formaldehyde (Figure 4) (11). It was expected that this methyl group would be significantly less prone to deprotonation than the simple proton-substituted compounds (12). Rather surprisingly, this did not prove to be the case. Reaction with acryloyl chloride in the presence of triethylamine at room temperature still resulted in a dark-brown mixture of products. Further, saponification of the Diels-Alder products using aqueous sodium hydroxide and methanol also resulted in extensive discoloration of the solution and reactions of the support. As a result, it is clear that a simple methyl group is not sufficient to prevent the base-mediated chemistry of the imidazolium ring in these cases.

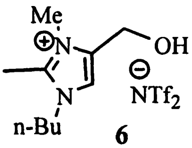

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Figure 4. 2-Methyl substituted fructose-derived RTIL support

Further evidence that these 2-methyl substituted imidazolium RTILs are not completely base stable came from a series of deuterium exchange experiments.

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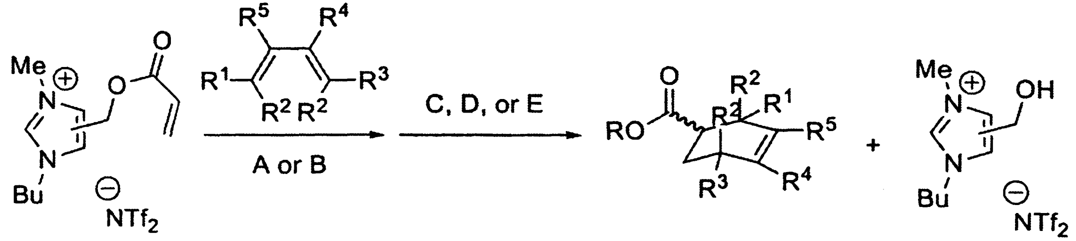
Table 1. Diels-Alder Sequence Results.



2 1

Entry	R^1	R^2	R^3	R^4	R^5	Conditions[a]	% Yield[b]	Endo/Exo[c]	% Recovered **1**
1	H	$-CH_2-$	H	H	H	A,C	60	3:1	97
2	H	H	H	Me	Me	B,C	63	NA	92
3[d]	H	H	H	Me	Me	B,C	57	NA	91
4	Me	H	H	H	H	B,C	46	5:1	90
5	H	$-(CH_2)_2-$	H	H	H	B,C	66	All endo	98
6	H	$-CH_2-$	H	H	H	A,D	78	3:1	92
7	H	$-CH_2-$	H	H	H	A,E	91	3:1	90

[a] A = Toluene, reflux, B = neat, hydroquinone, 120-140°C, C = KCN, MeOH, D = KCN, EtOH, E =KCN, BnOH.

[b] Isolated yield over three step sequence.

[c] Ratio determined by ^1H NMR.

[d] Using recycled ionic support **1**.

Treatment of RTIL **6** with triethylamine in D2O was sufficient to result in a slow, but detectible, exchange of the three protons on the methyl group (0.04 x 10^{-3} min^{-1}). Using potassium hydroxide instead greatly accelerated the rate of this exchange (2.3 x 10^{-3} min^{-1}). Similar results were obtained for the deuterium exchange of 1-butyl-2,3-dimethylimidazolium chloride or dicyanimide. As a result, it is clear that acid/base chemistry can occur at the methyl group of 2-methyl substituted imidazolium RTILs. Further effort will be required to address this limitation, possibly by further substitution of this site.

Supported Reagents/Catalysts

The other major area of supported synthesis is that of supported reagents and catalysts. Of the two existing reports, both have focused on supported catalysts. In one, a vanadyl salen complex was tethered to a RTIL for catalytic oxidations (13). In the other, a ruthenium metathesis catalyst was tethered to a RTIL (14). In both cases, these species were not only catalytically active, but were also readily retained in RTIL layers and thereby recycled.

Our particular interest was in the preparation of supported reagents, not catalysts. In particular, we viewed hypervalent iodine reagents such as diacetoxyphenyliodinane and Koser's salt as appealing challenges to the RTIL supported method (15). The reasoning behind this selection is twofold. First, reactions involving any of these reagents ultimately involve the separation of the iodobenzene by-product from the desired product. Although this can be accomplished via chromatography, it does preclude the direct use of the reaction products in subsequent reactions. This is particularly an issue in cases where the reaction products are sensitive and decompose on silica gel (*vide infra*). Second, these hypervalent iodine reagents are generated from iodobenzene. Although this same material can, in theory, be recovered at the end of the reaction, in practice it rarely is due to the extra effort required for recovery, purification, and regeneration. Thus, a large portion of the reagent becomes a waste material that must be discarded.

To address the issues associated with iodobenzene recycling, various supported iodinanes have been reported, most typically using polystyrene as the support (16). These supported reagents have been successfully applied in a number of cases and can be recycled. At the same time, they do suffer from the typical phase transfer problems that plague all hetereogeneous supports, thereby slowing the progress of these reactions. Further, the long term stability of polystyrene to these oxidizing agents is a concern as well.

Beginning with the fructose-derived RTIL **1**, acylation with p-iodobenzoyl chloride proceeded cleanly to afford supported iodobenzene **9** in nearly quantitative yield (Figure 5). Oxidation of this compound with peracetic acid under conditions similar to those reported for the preparation of diacetoxyiodobenzene resulted in the preparation of diacetoxy compound **7**.

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After the removal of all volatiles, the crude residue was used directly to prepare supported Koser's salt **8** by treatment with tosic acid in acetonitrile, again paralleling the procedure used for the parent, non-supported compound. Following removal of the volatiles, the resulting viscous liquid was used as is in subsequent reactions. ^{1}H NMR indicated the absence of any of iodo compounds **9** or **7**.

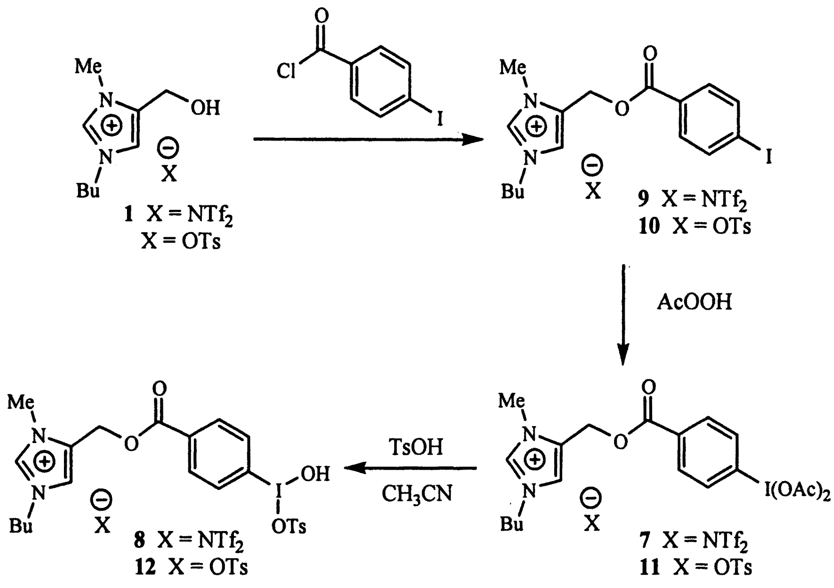

Figure 5. RTIL-supported Koser's salt

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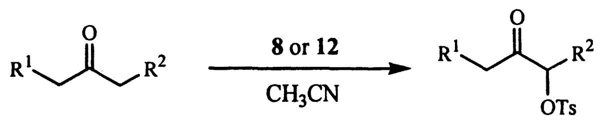
With the supported Koser's salt in hand, the α-tosyloxyation of ketones was studied (Table 2). Much to our delight, reagent **8** was effective for this transformation. The α-tosyloxyketones were obtained in >60% isolated yield. Further, the reactions themselves were faster than those with Koser's salt itself, likely due to the presence of the electron-withdrawing ester group on the benzene ring. The only problem was in the separation of supported iodobenzene **9** from the reaction products. This salt proved to be soluble in the same range of solvents as the tosyloxyketone products (ether, ethyl acetate, acetone, methylene chloride). Ultimately, the only effective method for separating the products from iodobenzene **9** proved to be chromatography. A quick separation using ethyl acetate/hexanes to elute the tosyloxyketone, followed by acetonitrile to elute salt **9** was reasonably effective and did result in 76-80% recovery of salt **9**. Still, the



need to use chromatography negated much of the potential advantage of this supported reagent.

Table 2. Tosyloxyation Results.

R^1	R^2	Conditions	Time	% Yield with 8[a]	% Yield with 12[a]
H	H	55°C,))))	30 min	67	60
CH_3	CH_3	55°C,))))	30 min	80	57
Ph	H	55°C,))))	30 min	74	74
-$(CH_2)_3$-		0°C	6 h	Decomp.	79
-$(CH_2)_2$-		55°C,))))	30 min	65	74

a). Isolated yield.

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Returning to the idea of RTILs having tunable physical properties, a potential solution was to employ a more hydrophilic salt. This could be most readily achieved by using a harder anion such as phosphate, tosylate, or chloride. To that end, supported iodobenzene **10**, which has a toluenesulfonate anion, was prepared (Figure 4). Oxidation with peracetic acid, followed by treatment with tosic acid in acetonitrile then afforded supported Koser's salt **12** as before. During this sequence, it was noted that all of the tosylate salts are more viscous than the triflimide salts. Further, salt **5** is actually a solid at room temperature.

With this second generation supported Koser's salt in hand, the α-tosyloxyation of ketones was again examined (Table 2). The reactions proceeded slightly slower than with the triflimide salt version of the supported Koser's salt, but were still generally complete within 30 minutes. The yields were comparable to those obtained before. The real advantage came in the separation phase. With tosylate salt **12**, the by-product was iodobenzene **10**, which could be readily separated by dilution of the reaction with ether. This reduction in polarity was sufficient to precipitate salt **10**, which could then be

recovered in >95% yield by simple filtration. The tosyloxyketone product could be isolated following an aqueous work-up on the organic layer. In most cases this afforded the pure product, but in some cases a trace of unreacted ketone was observed, which could be readily removed by trituration with cold hexane.

Importantly, the recovered iodobenzene **10** could be converted once again into the supported Koser's salt **12** as before. This material was again capable of carrying out the tosyloxyation reaction and afforded results indistinguishable from the initially prepared material. This recovery/reoxidation sequence could be carried out again and again, with no degradation of the support.

Conclusion

In conclusion, we have reported the application of a fructose-derived RTIL as a recyclable support for both reagents and reactants. Although not without limitations (particularly base stability), the ability to tune the solubility/miscibility properties of the support by changing the anion is an attribute unique to this family of supports. This feature greatly facilitates its recovery in the supported Koser's salt example and will undoubtedly be of value in a number of future applications of these and related supports. Further studies and applications of this concept are underway and will be reported in due course.

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Chapter 11

Ionic Liquid as a Support of Organic and Inorganic Catalysts

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Low lipophilicity, low hydrophobicity and low volatility are characteristic physical properties of room temperature organic ionic liquids (RMIL), which afford very independent nature to the liquids among others. This nature is expected to be useful as a support of homogeneous as well as heterogeneous catalysts for designing economically and environmentally friendly reactions. In the present study, potential utility of an ionic liquid as a support of catalysts was examined, in which following catalytic reactions were focused: nucleophilic reactions of unmodified aldehydes in an ionic liquid catalyzed by 1) a homogeneous organocatalyst, 2) a heterogeneous organocatalyst grafted on silica, and the Mizoroki-Heck reaction catalyzed by 3) a heterogeneous Pd catalyst in an ionic liquid, 4) a heterogeneous catalyst which immobilized a homogeneous Pd catalyst on silica by an ionic liquid. In all cases, mild, efficient and sustainable nature of the reactions has been demonstrated.

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Introduction

In view of green and sustainable aspects in organic synthesis, [1] a catalytic reaction with higher atom economy is desirable. [2] The use of environmentally benign reaction media is also desirable, because almost 2 million tons of organic solvents were used annually for production of organic materials. These requirements prompted synthetic organic chemists to employ catalytic reactions in green solvents.

In contemporary organic synthesis, a homogeneous catalyst was well investigated and a variety of highly sophisticated catalysts have been developed. Most homogeneous catalysts have established structures, which enables rational design of the catalyst by structural modification. As a result of structure tuning, higher reactivity and selectivity under milder reaction condition become possible. Disadvantage of a homogeneous catalyst is its instability. Most homogeneous metal catalysts are sensitive to heat, oxygen, moisture and so on. They easily loose catalytic activity forming metal clusters. These disadvantages made recycle use of the catalyst difficult, along with difficulty in catalyst separation from products and solvent. Efficient catalysts having high turn over number are not enough.

On the other hand, a heterogeneous catalyst has complementary character. They are stable, simple to separate, and thus easy to re-use. However, since structure is not always unambiguous, fine-tuning of the catalyst is not feasible.

Additional current interests in this area are revisit of synthetic organic chemists to an organocatalyst [3]. Since an organocatalyst does not involve any metal, there is no need to mind leaching out of metal. Design, tuning and reproduction of a catalyst might be easy without depending supply of metal from natural resource. However, compared to a metal catalyst, catalyst loading could not sufficiently be diminished. Low stability of an organocatalyst and recovery after the reaction is not suitable for recycle use.

Now, how do we approach to the preparation of the catalyst, which has higher reactivity along with stability and recyclability ? One conventional solution is to immobilize a known homogeneous catalyst in a liquid phase or on a solid material. As a liquid phase, non-volatile and non-mixing nature of ionic liquids [4] from other conventional organic solvents are expected to immobilize catalysts simply by dissolving a homogeneous catalyst, in which advantages of established catalysts could be utilized. [5]

In this article, our efforts on a facile and an efficient immobilization of a homogeneous as well as a heterogeneous catalyst in ionic liquid are described. These immobilized catalysts were successfully applied to two specific reactions, nucleophilic reactions of unmodified aldehydes and Mizoroki-Heck reaction.

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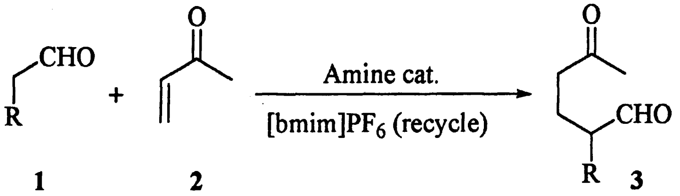
Nucleophilic Reaction of Unmodified Aldehyde in RMIL 1,4-Conjugate Addition by a Homogeneous Catalyst [6c]

Aldehyde has been used as a very versatile substrate for various synthetic transformations. In spite of its versatility as an electrophile, a role as a nucleophile has been quite limited because of difficulty to generate its enolate or enol ether quantitatively. Thus, nucleophilic reaction of aldehyde was carried out by transformation of the aldehyde into silyl enol ether or enamine beforehand, which is not always easy due to labile nature of the formyl group. We previously reported direct, highly efficient and very mild nucleophilic reactions of unmodified aldehydes in the presence of a catalytic amount of diehylaminotrimethylsilane (DEATMS) or diethylamine (DEA), without derivatization of the aldehydes. [6] Since wastes after the reactions were diethylamine, hexamethylsiloxane or water, the reactions were environmentally benign. Among the reactions, 1,4-conjugate addition of unmodified aldehyde 1 proceeded efficiently in acetonitrile. In designing sustainable process, highly polar ionic liquid is expected to be a candidate (Equation 1) as a recyclable solvent. Among ionic liquids, [bmim]PF_6 was employed because of very low lipophilicity and hydrophobicity that makes extraction with organic solvent as well as water easier. Air and moisture stabilities, easy availability and higher utility in several other organic reactions are additional reasons to choose.



Eq. 1

The reaction of aldehyde **1** with 3-buten-2-one **2** (MVK) was carried out in the presence of 0.2 equiv of the amine catalyst at 80 °C (Table 1). The product was partitioned into diethyl ether several times. After evaporation of the ether, pure 5-ketoaldehyde **3** was obtained by medium pressure LC purification. At room temperature or without amine, citronellal **1** was completely recovered. DEA was employed for further reaction because of better yields in the reaction with other aldehydes **1** (Table 1, entries 2 ~ 8) than the reaction with DEATMS. In entries 3 and 4, the 1,4-conjugate addition product **3** was directly isolated from [bmim]PF_6 by bulb to bulb distillation. The reaction condition is mild enough to give products **3** starting from the aldehydes **1** having acid or base sensitive protecting groups (Table 1, entries 6 ~ 8). The reaction was carried out simply in a test tube covered with septum in spite of highly volatile nature of

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DEA. Sealed tube technique was not required, which is another advantage in the reaction in ionic liquid.

[Bmim]PF_6 was re-used five times in DEA catalyzed reactions of citronellal **1** and MVK **2** in 62 ~ 71% yield, adding DEA freshly in each cycle.

Table I. 1,4-Conjugate Addition of Aldehydes 1 to 3-Buten-2-one 2 in [bmim]PF_6[a]

Entry	*Amine*	*Aldehyde 1* *R*	*Keto-aldehyde 3* *Yield (%)*
1	DEATMS	Me_2=$CH(CH_2)_2CHMeCH_2$	85
2	DEA	Me_2=$CH(CH_2)_2CHMeCH_2$	71
3	DEA	*i*-Pr	50[b]
4	DEA	C_8H_{17}	61(58)[b]
5	DEA	$PhCH_2$	60
6	DEA	$AcOC_8H_{16}$	56
7	DEA	$THPOC_8H_{16}$	68
8	DEA	$TBDMSOC_8H_{16}$	75

[a] Reaction was carried out with 0.2 equiv. of the catalyst at 80 °C under nitrogen.
[b] Product was distilled from [bmim]PF_6 *in vacuo*.

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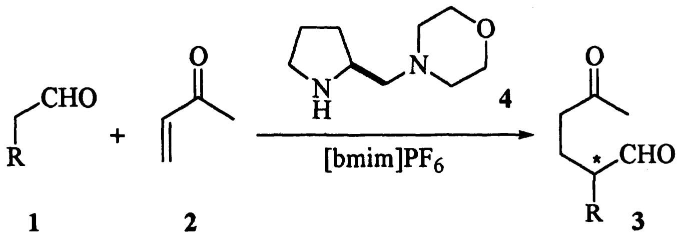
Catalytic asymmetric 1,4-conjugate addition by a homogeneous organocatalyst [7]



Eq. 2

The asymmetric conjugate addition of unmodified aldehyde **1** to MVK **2** was effected in [bmim]PF_6 to afford (2*S*)-5-keto-aldehyde **3** in up to 59% ee in the presence of 20 mol% of optically active pyrrolidine derivative **4** derived from L-proline (Equation 2, Table 2). Enantiomeric excess of the products were obtained by HPLC analysis of the corresponding benzoate **5**. The absolute stereostructure of **3** was determined to be *S* by Kusumi's PGME method after transformation of **3** into PGME-ester **6** (R = CH_2Ph) (Figure 1). Formation of the (3*S*)-keto-aldehyde **3** is explained by initial approach of MVK **2** to less hindered

Si-face of *E*-enamine 7 to avoid bulkiness of the morpholine residue on pyrrolidine ring (Figure 1). Use of ionic liquid was important to promote the reaction, since [bmim]PF_6 gave the highest chemical yield among other solvents such as DMI, DMSO or CH_3CN. Optically active cyclic amine based on L-proline resulted in higher enantiomeric induction at room temperature or below.

Table II. Catalytic Enantioselective1,4-Conjugate Addition of Various Aldehydes 1

Entry[a]	*Aldehyde 1*	*Keto-aldehyde 3*	
	R	*Yield (%)*[b]	*Ee (%)*
1	C_8H_{17}	29	42
2[b]	$PhCH_2$	29	59
3	$PhCH_2$	72	24
4	$AcOC_3H_6$	22	44
5	C_4H_9	46	42
6	$TBDMSOC_3H_6$	17	51

[a] All reactions were carried out at room temp. for 48 h in the presence of 0.2 equiv. of the diamine catalyst.

[b] Reaction was carried out at 2 °C without solvent.

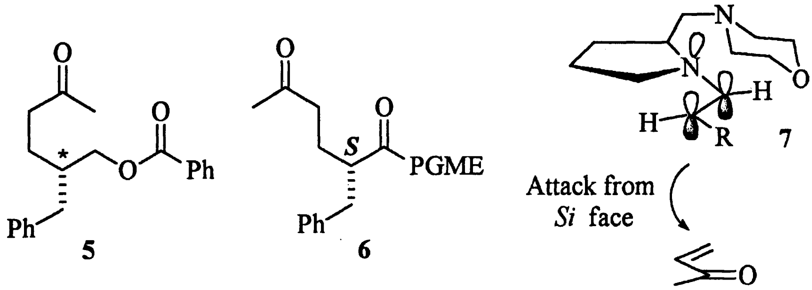


Figure 1.

1,4-Conugate Addition Catalyzed by a Heterogeneous Organocatalyst Grafted on Silica gel [8]

Since DEATMS or DEA was volatile and these catalysts should be added freshly in each recycle experiment, we investigated immobilization of amine residues on solid surface. Then, *N*-methylaminopropyl residue was grafted on amorphous and mesoporous silica gel (FSM-16) by a post modification method

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(Fig. 2) [9]. Employing the aminopropylated silica gel **8**, recyclable 1,4-conjugate addition reaction of citronellal **1** was possible (Equation 3, Table 3, entries 4 ~ 7) without any pre-treatment to re-activate the catalyst **8**. Heterogeneous amine catalyst grafted on the amorphous silica gel (NMAP-SiO_2) **8** (Fig. 2) was better than the catalyst grafted on mesoporous silica gel (NMAP-FSM) in [bmim]PF_6, while NMAP-FSM was active as a recyclable catalyst in toluene [10c].

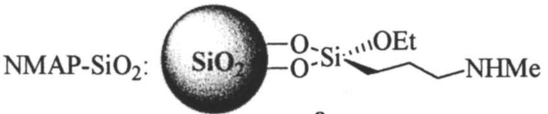

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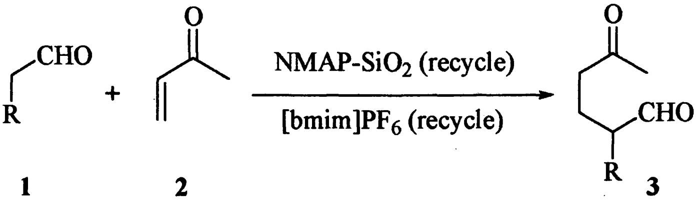
Figure 2 Amorphous N-methylaminopropylated silica gel



1 **2** **3**

Eq. 3

Table III. 1,4-Conjugate Addition of Citronellal 1 to 3-Buten-2-one 2 Catalyzed by Immobilized Organocatalyst in [bmim]PF_6[a]

Entry	*Catalyst*	*Keto-aldehyde 3 Yield (%)[b]*
1	–	0
2	NMAP-FSM[b]	20
3	NMAP-SiO_2[c]	62
4	NMAP-SiO_2[d]	49
5	2nd use	46
6	3rd use	59
7	4th use	57

[a] Reaction was carried out with 0.2 equiv. of the catalyst at 80 °C under nitrogen.
[b] Nitrogen content of per gram of the support was 0.5 mol/g.
[c] Nitrogen content of per gram of the support was 0.8 mmol/g.
[d] This system was recycled without pre-treatment for further reactions.

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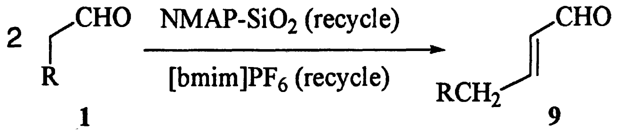
Self Aldol Condensation Catalyzed by a Hheterogeneous Organocatalyst Grafted on Silica gel [9]

There is no enough precedent on mild procedure of self-aldol condensation of unmodified aldehyde leading to α,β–unsaturated aldehyde (enal) **9** until DEATMS or DEA were found to catalyze the reaction by us. [6a] In order to develop more sustainable procedure, recycle of a catalyst as well as reaction media were investigated, in which NMAP-SiO_2 was revealed to catalyze the reaction in [bmim]PF_6 and the whole system could successfully be recycled (Equation 4). Representative results are compiled in Table 4. The reaction system continuously worked well until 8 recycles after heating the system *in vacuo* in order to remove H_2O generated in the previous aldol reaction. In cycle 7, inherent low reactivity of cross aldol reaction resulted in low yield. Actually, re-use of the same catalyst in cycle 8 for self-aldol condensation recorded higher yield back. In order to make decantation of the ether layer easier from lower ionic liquid layer on product isolation, cylindrical pellets which was grafted *N*-methylamino residue was used, since powdery NMAP-SiO_2 were floating between ether and ionic liquid layers during product partition. Mild nature of the present procedure is exemplified by the results that aldehydes **1** having acid or base sensitive substituents provided desired enals **9** in satisfactory yields (entries 8 ~ 10).



Eq. 4

The heterogeneous aminopropylated silica gel **8** and congeners were effective as catalysts not only for nucleophilic reactions of unmodified aldehyde [10] but also for various synthetic transformations such as Knoevenagel condensation [11] or ester metathesis [12].

Mizoroki-Heck Reaction in RMIL

Mizoroki-Heck Reaction Catalyzed by Hhomogeneous Pd Catalyst

Mizoroki-Heck reaction has been one of the most fundamental Pd-catalyzed carbon-carbon bond forming reaction [13]. Since its invention, numerous efforts have been devoted to further development of the reaction because of its usefulness and especially the wide applicability to various substrates. Recent developments in this area enabled the introduction of various new ligands, new bases, new techniques such as microwave or ultra sonic irradiation and so on. [14]

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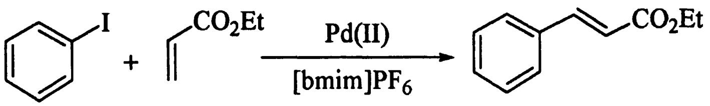
Table IV. NMAP-SiO$_2$ Catalyzed Self-aldol Condensation of Aldehyde 1 in [bmim]PF$_6$

Entry[a]	*Aldehyde 1* *R*	*Time (h)*	*Enal 9* *Yield (%)*[c]
1[b]	C_8H_{17}	5	83
2	C_8H_{17}	5	70
3	C_8H_{17}	5	82
4	C_8H_{17}	5	81
5	C_8H_{17}	5	70
6	$PhCH_2$	21	81
7	Cross aldol[d]	19	22
8	$TBDMSOC_3H_6$	7	82
9	$THPOC_8H_{16}$	20(5)[e]	58(78)[e]
10	$AcOC_3H_6$	24	44
11	$AcOC_3H_6$	48	51

[a] Reaction was carried with 0.2 equiv. of the catalyst at 80 °C in [bmim]PF$_6$ under nitrogen atmosphere.
[b] After entry 1, the same reaction system was evacuated at 1.5 mmHg at 70 °C and re-used for subsequent reaction.
[c] Yields were for isolated pure products by decantation with ether followed by medium pressure LC.
[d] Reaction of *p*-nitrobenzaldehyde and acetone (10 equiv.) gave *p*-nitrtobenzalacetone.
[e] New catalyst was used.

Another current interest is the development of environmentally benign reaction conditions. To this end, reactivities of several homogeneous palladium catalysts were investigated in [bmim]PF$_6$ (Equation 5). As shown in Table 5, entries 1 ~ 3, the homogeneous catalysts afforded satisfactory results without ligand in the ionic liquid. Earle and his co-workers, including recycle use of the catalyst solution, reported further work on the reaction. [15]



10 11 12

Eq. 5

In Ionic Liquids in Organic Synthesis; Malhotra, S.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2007.

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Table V. Ligandless Mizoroki-Heck Reaction with Homogeneous Catalyst

Entry[a]	*Pd catalyst*	*Time (h)*	*Cinnamate 12 Yield (%)*
1	$Pd(OAc)_2$	24	91
2	$PdCl_2(PPh_3)_2$	12	95
3	$PdCl_2$	12	93

[a] Reaction was carried out at 100 °C without ligand.

Mizoroki-Heck Reaction Catalyzed by Pd/C [16]

In view of economy of the reaction, the recovery as well as recycling of the expensive Pd catalyst is desired. However, a homogeneous Pd catalyst usually precipitated from the solution and recycling or recovery of an active Pd catalyst was difficult. Heterogeneous catalysts would be much better from viewpoint of recycle use. Pd/C is a recoverable heterogeneous catalyst and is stable and relatively inexpensive, although its catalytic activity was under developed except in catalytic hydrogenations. Thus, we have focused on Mizoroki-Heck reaction in an ionic liquid, in which highly polar nature of an ionic liquid is expected to work as an activating and stabilizing solvent for Pd/C-catalyzed Mizoroki-Heck reaction.

The reaction was carried out simply by heating a solution of aryl iodide **10**, olefin **11** and base with 5 mol% of 10%–Pd/C which dispersed well in $[bmim]PF_6$. After the reaction, the product was extracted simply by stirring with *n*-hexane or diethyl ether several times followed by decantation of the upper organic layer. Isolation of the product from the ionic liquid was complete according to GLC analysis of the ionic liquid remained. The Pd/C was kept and suspended only in the ionic liquid layer after the extraction.

Some representative results are compiled in Table 6. As shown in entries 1 ~ 3, ethyl cinnamate **12** was obtained in satisfactory yields. Aryl iodides **10** having electron donating or –withdrawing substituents gave the corresponding cinnamates **12**. Among the bases investigated, triethylamine gave the best result. An inorganic base such as sodium hydrogen carbonate provided poor yields. Bromobenzene **10** also gave ethyl cinnamates **12** as shown in entries 5 and 6, though aryl triflates were recovered completely even at 140 °C with phosphine ligand. Not only acrylate **11** but also acrylonitrile **11** (entries 8 and 9), methyl methacrylate **11** (entry 10) and styrene **11** (entries 11 and 12) provided the products. In entry 1, leaching of Pd was 0.31 ppm according to ICP analysis.

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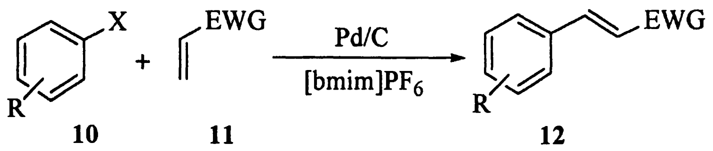


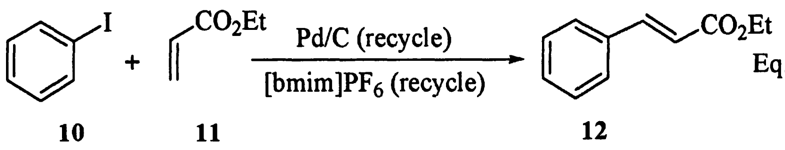
Eq. 6

Table VI. Pd/C Catalyzed Mizoroki-Heck Reaction in [bmim]PF_6

Entry[a]	*Arylhalide 10*		*EWG*	*Cinnamate 12*
	X	*R*		*Yield (%)*
1	I	H	CO_2Et	95
2	I	COMe	CO_2Et	65
3	I	OMe	CO_2Et	69
4	I	Br	CO_2Et	66
5[b]	Br	H	CO_2Et	40
6[b]	Br	NO_2	CO_2Et	85
7	CH=CHBr	H	CO_2Et	49
8	I	H	CN	74(18)[c]
9	I	OCH_3	CN	69(19)[c]
10	I	H	Me, CO_2Me	70
11	I	Me	Ph	59
12	I	OCH_3	Ph	59

[a] Reaction was carried out at 100 °C without ligand.
[b] Reaction was carried out at 140 °C without ligand.
[c] Amount of *Z* isomer accompanied.

Under conventional reaction conditions, a homogeneous Pd catalyst deteriorated and Pd black deposited after the reaction. Recovery of the Pd catalyst usually is not realistic, thus eliminating the possibility of recycling the Pd catalyst. In the present reaction, since Pd/C remained only in the ionic liquid layer, the ionic liquid containing Pd/C can be re-used as a catalyst system (Equation 7, Table 7). Although certain amount of decrease of yields were observed after the second reuse (entries 3 ~ 5), probably due to accumulation of triethylammonium iodide, washing the ionic liquid layer with water recovered the catalytic activity to the same level as the fresh system (entry 6).



Eq. 7

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Table VI. Recycling of Pd/C and [bmim]PF_6

Entry[a]	*Yield (%)*
1	92
2	93
3	84
4	81
5	80
6[b]	95

[a] Reaction was carried out under the reaction conditions as described in Table 6, entry 10.
[b] The catalyst was washed with water.

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Mizoroki-Heck Reaction Catalyzed by Heterogeneous Catalyst which was Immobilized Homogeneous Pd Catalyst on Silica gel by RMIL [17]

As described in the previous sections, the ionic liquid have played an effective role as a liquid support of homogeneous as well as heterogeneous catalysts since simply mixing catalysts in ionic liquid is sufficient to immobilize catalysts. No multi step procedure such as polymerization or sintering is required. In addition, knowledge on the catalyst developed so far could be fully utilized.

One disadvantage of the protocol is the cost of an ionic liquid as a liquid support. In order to minimize the amount of ionic liquid as a support, immobilization of a catalyst was investigated with the aid of an ionic liquid layer on silica gel, which is chemically and mechanically stable. Immobilization of the Pd catalyst in this way should provide the following features: 1) immobilization is easy 2) immobilization is inexpensive without using expensive coupling reagents or a large amount of ionic liquid, 3) the Pd catalyst is stabilized in ionic liquid layer, 4) work up procedure, especially isolation of the product is easier than extraction from viscous ionic liquid.

The procedure of immobilization is very simple. A suspension of spherical amorphous silica gel in a solution of $Pd(OAc)_2$ in [bmim]PF_6 and THF was evaporated to dryness to afford a powdery and free-flowing immobilized catalyst. Not only $Pd(OAc)_2$ but also $Pd(PPh_3)_4$ and Pd black could be immobilized on silica gel according to this procedure. Among ionic liquids tested, [bmim]PF_6 was better to hold $Pd(OAc)_2$ than [bmim]Br, [bmim]$(CF_3SO_2)_2N$, or [hmim]PF_6.

The immobilization of a homogeneous catalyst with an ionic liquid on a surface of silica gel was pioneered by Mehnert *et al.*, who demonstrated immobilization of a rhodium catalyst in [bmim]PF_6 on a silica gel surface [18].

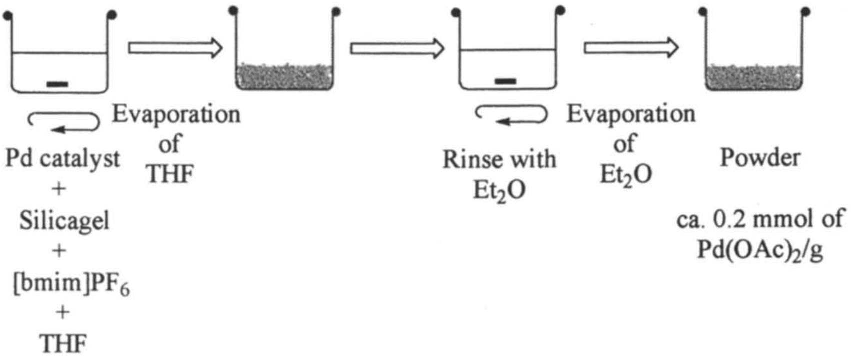

Fig.3. Procedure for immobilization

This method of immobilization attracted much attention of chemists. Actually, Han *et al.* supported Pd nanoparticles on molecular sieves by an ionic liquid and applied to hydrogenation catalyst. [19]

The surface of the immobilized silica gel was observed by several analytical procedures. According to scanning electron microscopy (SEM), the shape of the immobilized catalyst was observed to be round and the surface was smooth (Fig. 4).

In contrast to the original unsupported silica gel, primary particles were observed clearly in a magnified picture (Fig. 5), which indicates that ionic charges exist on the round surface or in the pores of the primary silica gel particles.

Electron probe microanalyses (EPMA) showed that phosphorus, fluorine as well as Pd distributed on the surface of silica gel uniformly (Fig. 6).

Smooth surface of the supported silica gel was observed compared to that of unsupported silica gel in pictures of atomic force microscopy (AFM) (Fig. 7). Inspection of these pictures, the amount of [bmim]PF_6 used, along with dry and free flowing character of the immobilized catalyst, suggest that the solution of $Pd(OAc)_2$ in [bmim]PF_6 exists in the pores of silica as shown in Fig. 8.

By employing a reaction of iodobenzene **10** and ethyl acrylate **11** as a probe, the reaction conditions were optimized (Table 8). In order to prevent removal of the ionic liquid layer from the immobilized catalyst **13**, the reaction was carried out in a hydrocarbon solvent.

Among Pd sources, $Pd(OAc)_2$ was chosen for further reactions due to the lack of poisonous phosphine ligand, stability and economy since $Pd(OAc)_2$ and $Pd(PPh_3)$ showed similar activities as shown in entries 2 and 3. Triethylamine was a superior base than potassium carbonate. Re-use of the catalyst **13** was difficult in hot toluene due to the solubility of the ionic liquid on silica gel. Addition of sodium *m*-diphenylphosphinobenzenesulfonate as a recyclable ligand did not show significant improvement (entry 5). With cyclohexyl acrylate **11**, the yield was improved in a certain amount (entry 7). When the reaction temperature was raised to 150 °C in a sealed tube, the reaction proceeded almost quantitatively (entry 8). Finally, the optimized reaction condition was obtained using tri-*n*-butylamine as a base in an open vessel (entry 9).

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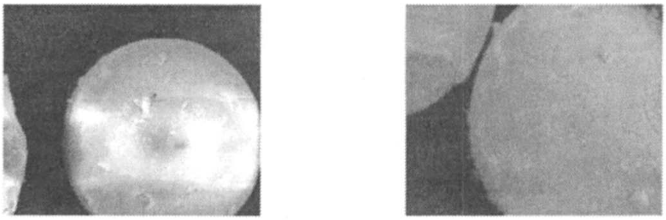
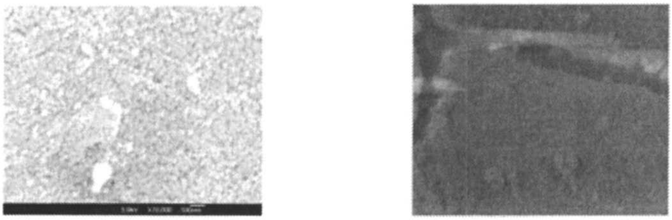


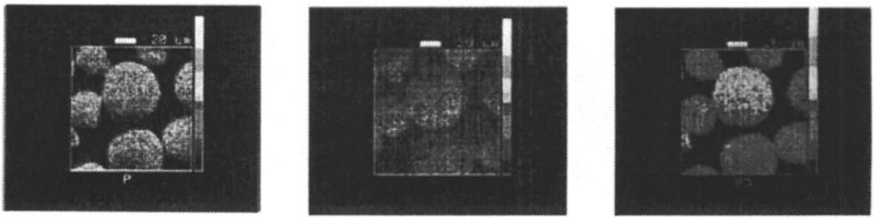
Supported (10 Kv, x 1,700) Unsupported (5 Kv, x 1,900)

Figure 4. Images of scanning electron microscopy (SEM) of supported and unsupported silica gel



Supported Unsupported

Figure 5. Magnified images of SEM of supported and unsupported silica gel (5 Kv, x 70,000)



Phophorous Fluorine Palladium

Figure 6. Images of electron probe microanalyses (EPMA) of supported silica gel

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In Ionic Liquids in Organic Synthesis; Malhotra, S.;
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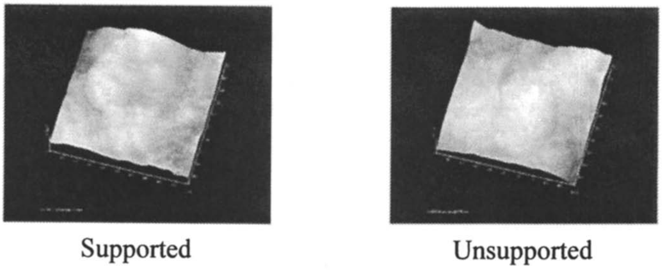
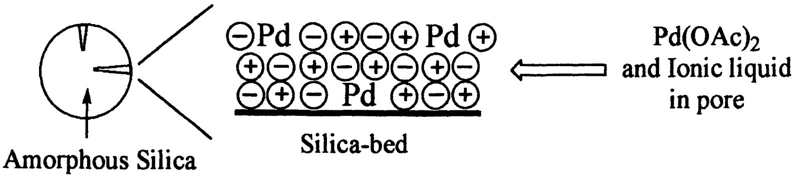


Figure 7. Images of atomic force microscopy (AFM) of supported and unsupported silica gel (500 nm x 500 nm)



13

Figure 8.Immobilization of ionic liquid layer in silica gel pore

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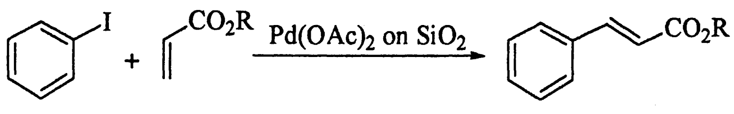


10 11 12

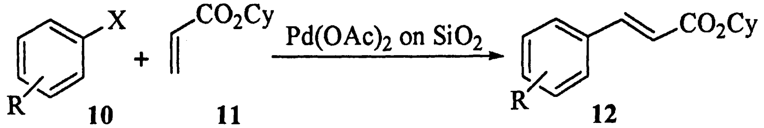
Eq. 8

Table VIII. Optimization of Reaction Condition

Entry[a]	*Acrylate 11 R*	*Catalyst*	*Solvent*	*Time (h)*	*'innamate 12 Yield (%)*
1	Me	Pd black	*n*-Dodecane	7.0	31
2	Me	$Pd(PPh_3)_4$	*n*-Dodecane	7.0	59
3	Me	$Pd(OAc)_2$	*n*-Dodecane	7.0	59
4	Me	$Pd(OAc)_2$	Methylcyclohexan	5.0	22
5[b]	Me	$Pd(OAc)_2$	*n*-Octane	7.5	51
6	Me	$Pd(OAc)_2$	*n*-Dodecane	5.0	51
7	Cyclohexyl	$Pd(OAc)_2$	*n*-Dodecane	16.5	75
8[c]	Cyclohexyl	$Pd(OAc)_2$	*n*-Dodecane	16.5	99
9[d]	Cyclohexyl	$Pd(OAc)_2$	*n*-Dodecane	15.0	96

[a] Reaction was carried out at 120 °C with 2 equiv. of Et_3N.
[b] Sodium *m*-diphenylphosphinobenzenesulfonate was added with 2 equiv. of olefin.
[c] Reaction was carried out in a sealed tube at 150 °C.
[d] Reaction was carried out with 2 equiv. of *n*-Bu_3N at 150 °C in an open vessel.

According to the optimized reaction condition (Table 8, entry 9), the Mizoroki-Heck reaction with several aryl halides **10** was examined and some representative results are listed in Table 9. Not only aryl halides having electron-withdrawing substituents but also those having electron-donating substituents provided coupling products in satisfactory yields (entries 1 ~ 4). In entry 6, a certain amount of reduction of the starting material proceeded. In entry 7, arylbromide gave the product. It is worthy of note that the rate of the reaction increased compared to the reaction with homogeneous system, $Pd(OAc)_2$ in $[bmim]PF_6$ (Table 5, entry 1).



10 11 12

Eq. 9

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Table IX. Mizoroki-Heck Reaction with Various Aryl Halides 1 with Cyclohexyl Acrylate 2

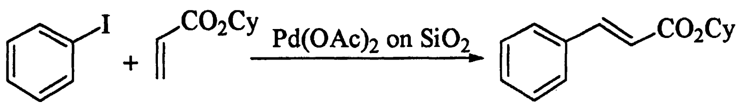
Entry[a]	*Arylhalide 10*		*Time (h)*	*Cinnamate 12 Yield (%)*[b]
	X	*R*		
1	I	4-Br	1.3	82
2	I	4-Ac	1.3	81
3	I	4-MeO	2.5	96
4	I	4-Me	2.0	86
5	I	4-I	5.0	68
6	I	2-CHO, 4-MeO, 5-OH	2.0	57[c]
7	Br	4-NO_2	3.0	86
8	2-Iodothiophene		8.0	31
9	1-Iodonaphthalene		2.5	88

[a] Reaction was carried out under the optimized reaction condition as described in Table 8, entry 9.
[b] Yield is for isolated pure product and is based on aryl halide **10**.
[c] Product **12** was accompanied with vanillin in 17% yield.

The immobilized catalyst **13** was easily re-used up to 3 times without any pre-treatment after taking up the supernatant *n*-dodecane layer (Table 10). A decrease of the catalytic activity was observed after 3 recycles (entries 4 and 5), in which the free-flowing nature of the catalyst was lost. This result might arise from covering the silica gel surface with resulting tributylammonium iodide, which could not be removed due to its insolubility in *n*-dodecane. Washing the catalyst 13 with dil. aq. sodium hydroxide to retrieve the catalytic activity as shown in entry 6 solved this shortcoming.

In the reaction of iodobenzene **10** and cyclohexyl acrylate **11**, the turnover number (TON) and turnover frequency (TOF) reached 90,000 and 5,000 (h^{-1}), respectively (Equation 10, Table 11, entry 5), which are very high figures among other phosphine free heterogeneous Pd catalysts. [20] By recycling the catalyst, the TON could be multiplied. $Pd(OAc)_2$ in the pores distributed on the wide surface area of the silica gel might provide the remarkably high efficiency.

The supernatant *n*-dodecane layer was filtered through a membrane filter (pore diameter: 7 μm) after the reaction and the mixture was analyzed by ICP, in which 0.28 ppm of Pd was found in the layer when 10 mol% of $Pd(OAc)_2$ was used in the reaction. The level of leaching is quite reasonable compared to other heterogeneous Pd catalysts supported on solid.



10 **11** **12**

Eq. 10

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Table X. Recycling of the Immobilized Catalyst 13

Entry[a]	*Yield (%)*
1	96
2	98
3	96
4	90
5	89
6[b]	93

[a] Reaction was carried out under the optimized reaction condition as described in Table 8, entry 9.

[b] The catalyst was washed with dil. aq. NaOH.

Table XI. Performance of the Immobilized Catalyst 13

Entry	*Catalyst (mol%)*	*Time (h)*	*Yield (%)*	*TON*	*TOF (h^{-1})*
1	1.03	5.5	91	88	16
2	0.53	6.0	96	180	30
3	0.24	8.0	91	380	48
4	0.13	8.5	94	720	85
5	0.0004	20.0	35	90,000	5,000

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Conclusions

We have demonstrated that room-temperature ionic liquids are very useful and conventional tools to immobilize organic as well as inorganic catalysts. Especially, immobilization of homogeneous catalyst on the surface of silica gel with the aid of ionic liquid would have wide applicability towards various catalytic reactions due to its easy procedure for preparation.

Acknowledgments

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Chapter 12

Ionic Liquids Applications in Green Chemistry: Copper and Zinc Catalysis

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Zinc-containing ionic liquids are good catalysts for Diels-Alder, Fischer indole and Pictet Spengler reactions; copper bisoxazolines are enantioselective catalysts for Diels-Alder and cyclopropanation reactions in ionic liquids, in some cases the catalysts can be reused.

Metal Based Ionic Liquids

The first metal-based ionic liquids (the term ionic liquid has been used to describe salts that melt below 100 °C (*1*)) were prepared by Hurley and Weir who mixed pyridinium halides with aluminum chloride (*2*). Further interest in chloroaluminate ionic liquids arose from the use of mixtures of 1-alkyl-3-methylimidazolium chlorides with aluminium chloride which had improved electrochemical and physical properties (*3*). The composition of chloroaluminate ionic liquids can be varied by using different ratios of ammonium halide and aluminium chloride. This in turn affects the chemical properties, varying from Lewis basic with an excess of the ammonium halide, to Lewis acidic with an excess of aluminum chloride.

Chloroaluminate ionic liquids have found application as reaction media for several Lewis acid catalysed processes (*1*). However, a major drawback of these

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liquids is their moisture sensitivity; their preparation and use requires strictly anhydrous conditions and removal of the products often involves quenching the reaction with water which has to be done with care due to the high reactivity of the aluminium chloride. In addition, this process destroys the ionic liquid. Hence, there has been interest in developing other metal-based ionic liquids which are Lewis acidic but less sensitive to moisture. For example, in recent years ionic liquids based on mixtures of pyridinium, imidazolium or ammonium halides and $FeCl_n$ (n = 2,3), (*4*) $SnCl_2$(*5-7*) and $ZnCl_2$ (*5,8,9*) have been reported. Mixtures of [BMIM]Cl (BMIM = 1-butyl-3-methylimidazolium) and $ZnCl_2$ were first reported by Dupont *et al* (*9*) and these were used to immobilise $RuCl_2(PPh_3)_3$ for the biphasic hydrogenation of 1-hexene.

Table 1. The effect of mole fraction (x) of $ZnCl_2$ on the melting point and viscosities of mixtures of [BMIM]Cl and $ZnCl_2$

(x) mole fraction of $ZnCl_2$	*M. Pt. (°C)*	*Viscosity*
0.5	1	3524
0.6	3	6440
0.67	13	18040
0.71	18	61040

The organo-zincate ionic liquids were prepared by mixing appropriate amounts of [BMIM]Cl and $ZnCl_2$ and heating to 100 °C until all the solid had melted. The melting points and viscosity were measured after cooling and depend on the mole fraction of $ZnCl_2$ (Table 1). These melting points are 60-90 °C lower than those reported earlier (*9*). The most likely explanation for this is that our liquids contain traces of water. Although we used *anhydrous* $ZnCl_2$ no attempt was made to further dry this before use. In addition, though Schlenk techniques were used, the transfer of solids to the Schlenk tubes was done in air rather than in a dry box. The liquids were dried under vacuum overnight (at 65 °C) after synthesis before measuring the melting points, however we made no attempt to measure the residual water in these liquids. Since the purpose of this work was to find water-tolerant metal-containing ionic liquids no further attempts to reduce the water content were made. We have previously noted that up to four equivalents of water with respect to zinc can be added to zinc-containing ionic liquids with little or no effect on their ability to catalyse Diels-Alder reactions (*10*). The presence of some water does decrease the viscosity of the liquids.

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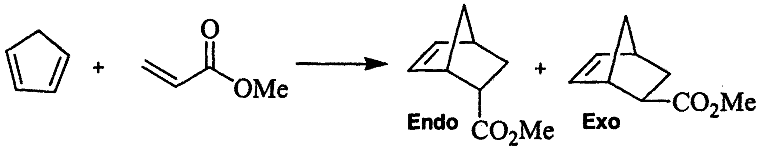
The FAB mass spectrum of [BMIM]Cl-$ZnCl_2$ shows the presence of $ZnCl_3^-$, $Zn_2Cl_5^-$ and $Zn_3Cl_7^-$. The viscosity increases with the proportion of $ZnCl_2$ as expected since the increased size of the anions decreases their mobility (*7*).

As mentioned above several reactions have been reported in chloroaluminate ionic liquids however there the only reports of organic synthesis in chlorozincate salts are our previous work on Diels-Alder reactions (*10*) and Fischer indole syntheses (*11*) in choline chloride:$ZnCl_2$ mixtures. Here we describe the use of [BMIM]Cl : $ZnCl_2$ mixtures as media for Diels-Alder, Fischer indole and Pictet Spengler reactions.

Diels-Alder Reactions in [BMIM]Cl : $ZnCl_2$ mixtures

The Diels-Alder reaction between cyclopentadiene and methyl acrylate was chosen as a model reaction since solvent effects on this reaction have been extensively studied.* The results are shown in Table 2.



The results show that increasing x has a profound effect on the *endo*:*exo* ratio. The ratio of approximately 7 in a neutral melt reflects the polarity of the medium and is similar to the ratio found in methanol.* The ratio of over 15 when x = 0.71 reflects the increased Lewis acidity of the medium. A similar *endo*:*exo* ratio was found previously using 5 mol% ZnI_2 dissolved in [BMIM][PF_6].

Table 2. The effect of mole fraction (x) of $ZnCl_2$ on selectivity in the Diels-Alder reaction of methylacrylate and cyclopentadiene

x	*endo*:*exo*[a]	*Yield %*[b]
0.5	7.2	84
0.6	11.1	82
0.67	14.9	84
0.71	15.6	89

[a]Determined by ^1H NMR

[b]Determined by ^1H NMR using ferrocene as an internal standard

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However the ratio is much higher than was observed with the choline chloride:$ZnCl_2$ ionic liquids (*10*).

The reaction is biphasic and the products can be removed by decantation from the rather viscous ionic liquid, any residual product can be extracted with diethyl ether. After removal of the products fresh substrates were added to the ionic liquid and the reaction repeated. The ionic liquid could be reused at least five times with negligible decrease in yield and selectivity demonstrating that the ionic liquid is acting as a catalyst. Whilst in principle this can be done with the corresponding chloroaluminate liquids their extreme moisture sensitivity means the entire process would need to be carried out in a dry atmosphere.

Fischer Indole Reactions in [BMIM]Cl : $ZnCl_2$ mixtures

The Fischer indole synthesis has been studied in great detail and is widely used in the large scale production of a number of indole containing products (*12*). The reaction involves cyclisation of a phenylhydrazone formed by condensation of phenylhydrazine and a ketone. The reaction is usually catalysed by weak Bronsted or Lewis acids, though excess of the acid is often used. To our knowledge there are only two previous reports of Fischer indole syntheses in ionic liquids; the first used 1-butylpyridinium chloride-(x)$AlCl_3$ (x = 0.67) and showed that indoles could be synthesised in high yield though work-up destroyed the ionic liquid (*13*). More recently we reported the use of choline chloride-(x)$ZnCl_2$ (x = 0.67) to synthesise a number of indoles with removal of the product by sublimation and reuse of the ionic liquid (*11*). Our initial study examined the synthesis of 2-phenylindole from the preformed hydrazone. The hydrazone was heated at 100 C for 12 hours in [BMIM]Cl-(x)$ZnCl_2$ (x = 0.67). Extraction of the product with ether gave an almost quantitative yield of 2-phenylindole. Alternatively, the product could be sublimed directly from the ionic liquid in 95% yield. The one-pot reaction starting from acetophenone and phenyl hydrazine was then examined in ionic liquids conatining varying amounts of $ZnCl_2$ (x = 0.5 to 0.71). In all cases the reaction mixture was stirred at 100 °C. After 1 hour the formation of the intermediate phenylhydrazone was complete in all the ionic liquids. However formation of the final product, 2-phenylindole, was faster in the ILs containing more $ZnCl_2$ and was complete in only 8 hours in [BMIM]Cl-(x)$ZnCl_2$ (x = 0.71). Even though the reaction is slower for lower values of x, quantitative conversion of the hydrazone to 2-phenylindole was observed in all cases with longer reaction times.

The scope of the reaction in [BMIM]Cl-(x)$ZnCl_2$ is shown in Table 3. Surprisingly the reactions gave fewer side products and higher yields starting from the hydrazine and ketone rather than the preformed hydrazone.

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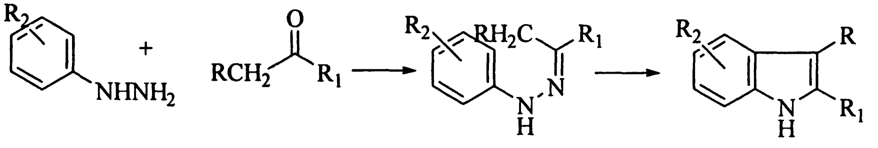

Table 3 Fischer indole synthesis in [BMIM]Cl-(x)$ZnCl_2$ (x = 0.71)

ketone	*R_2*	*Product*	*Yield %*
R = H, R_1 = Ph	H	2-phenylindole	93
R = R_1 = Me	H	2,3-dimethylindole	94
R = R_1 = Me	*o*-Me	2,3,7-trimethylindole	90
R = R_1 = Me	*p*-Cl	5-chloro-2,3-dimethylindole	88
R = R_1 = Me	2,5-Cl_2	4,7-dichloro-2,3-dimethylindole	73
R + R_1 = $(CH_2)_3$	H	1,2,3,4-tetrahydrocyclopenta[b]indole	90
R + R_1 = $(CH_2)_4$	H	1,2,3,4-tetrahydrocarbazole	93
R + R_1 = $(CH_2)_4$	*o*-Me	8-methyl-1,2,3,4-tetrahydrocarbazole	72
R + R_1 = $(CH_2)_4$	*p*-Cl	6-chloro-1,2,3,4-tetrahydrocarbazole	80
R + R_1 = $(CH_2)_5$	H	5,6,7,8,9,10-hexahydrocyclohepta[b]indazole	91

In all cases good yields of products were obtained and in most cases the product could be easily isolated by vacuum sublimation. For indoles that proved difficult to sublime, addition of water and extraction with dichloromethane allowed isolation of the product. The reaction works well with dialkyl ketones and cyclic ketones and with chloro or methyl substituents on the phenylhydrazine.

An important issue in the Fischer indole synthesis is the regioselectivity when an unsymmetrical dialkyl ketone is used. Thus the reaction of phenylhydrazine and butanone can give 2,3-dimethylindole or 2-ethylindole or more usually some mixture of both. We observed exclusive formation of 2,3-dimethylindole in 94% yield. This is consistent with our previous observation of formation of only this product in the related choline chloride-$ZnCl_2$ ionic liquid (*11*). We postulate that this selectivity is due to stabilisation of the intermediate iminium cation leading to formation of the thermodynamically favoured more substituted enamine.

The recyclability of the IL was examined for the reaction between butanone and phenylhydrazine. After isolation of the product by vacuum sublimation more

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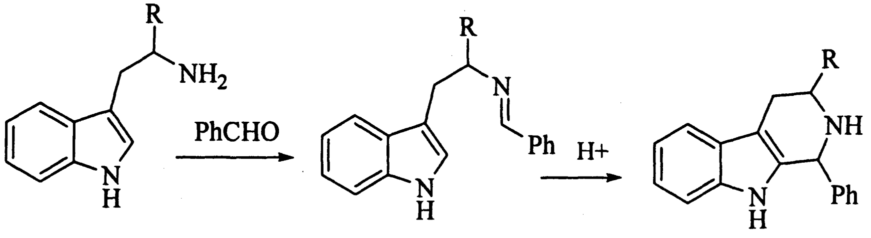
butanone and phenylhydrazine were added and the reaction was repeated giving an almost identical yield. However, on subsequent runs the yield dropped and was about 54% on the fifth run.

Pictet Spengler Reaction Reactions in [BMIM]Cl : $ZnCl_2$ mixtures

The Pictet-Spengler reaction generally refers to the condensation of tryptamines or tryptophans with aldehydes or ketones to give β-carbolines and is the method of choice for synthesis of these heterocycles (*14*). The reaction proceeds via formation of an imine which undergoes acid catalysed attack on the indole ring. The catalyst is usually a Bronsted acid. Recently Lewis acid catalysed versions have been reported, notably [BMIM]Cl-(x)$AlCl_3$ (x = 0.5) was found to be a highly active catalyst for the formation of **1** (*15*). An 80% yield of **1** was obtained at room temperature after 24 hours. Extending these results to the less reactive tryptamine was less successful requiring 10 mol%$Yb(OTf)_3$ and 50 mol% [BMIM]Cl-(x)$AlCl_3$ (x = 0.5). We investigated the reaction of tryptamine with benzaldehyde using [BMIM]Cl-(x)$ZnCl_2$ (x = 0.67) as solvent and catalyst.



1 R = CO_2Me
2 R = H

Tryptamine was added to an equimolar amount of [BMIM]Cl-(x)$ZnCl_2$ (x = 0.67) and stirred at 60 °C before addition of 1.2 equivalents of benzaldehyde. The reaction mixture was stirred at 100 °C for 16 hours after which time TLC and GCMS showed complete consumption of the tryptamine. After cooling the reaction mixture solidified which made extraction difficult. Addition of water to dissolve the ionic liquid followed by extraction with dichloromethane gave a reasonable yield of product **2** (55%). In order to facilitate recycling of the ionic liquid the reaction was repeated using 1,2-dichloroethane as a cosolvent. The reaction was stirred at 80 °C for 24 hrs. After cooling to room temperature the ionic liquid layer formed a gel allowing decanting of the organic layer and washing of the ionic liquid layer with more 1,2-dichloroethane. The product was

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isolated in about 70% yield. The ionic liquid was then dried under vacuum at 80 °C before addition of fresh substrates. The reaction could be repeated five times with only a small drop in yield.

Asymmetric Copper Catalysis in Ionic Liquids

Copper bis(oxazoline) complexes have attracted much attention in the last ten years due to their application as chiral catalysts for a wide range of organic reactions (*16*). As a consequence there has been increasing interest in the immobilisation of such complexes via covalent attachment to an organic polymer or to silica or ion-pairing with an anionic support to provide easy separation of the catalyst from the products and even recovery and reuse of the catalyst (*17*). In all cases the immobilisation exerts a significant influence on the outcome of the reaction, often with a reduction in the enantioselectivity. Hence there is a need for immobilisation methods that have less influence on the catalyst enantioselectivity.

Immobilisation in a liquid phase rather than attachment to a solid support may reduce the influence of the support. Recently perfluoroalkyl-substituted bisoxazolines have been used to produce a fluorous biphase compatible catalyst (*18*). Ionic liquids have attracted increasing interest when used in a biphasic system for the separation and recycling of metal-containing catalysts (*19-21*). The catalyst remains in the ionic liquid phase and in some cases can be reused several times with little reduction in activity. This approach has also been applied in asymmetric catalysis (*22*). including two examples of copper catalysed cyclopropanation (*23,24*) We have investigated copper bisoxazoline catalysed cyclopropanation and Diels-Alder reactions in [BMIM][PF_6], [BMIM][OTf], [BMIM][BF_4], [BMIM][NTf_2]. The primary objective was to establish whether ionic liquids would provide an effective means of recovery and reuse of the catalyst while maintaining or even improving catalysts efficiency. Some of these results have been reported previously (*24*).

Asymmetric Cyclopropanation

Evans *et al.* reported that cyclopropanation of styrene with ethyl diazoacetate in chloroform catalysed by the complex of bis(oxazoline) **1** with copper(I) triflate (Scheme 1) gave the *trans* and *cis* cyclopropanes in a 73: 27 ratio and 99 and 97% *ee* respectively (*25*). They also showed that the catalytic activity and enantioselectivity was dependent on the nature of the anion associated with the copper (*25*). Under our conditions the *trans* : *cis* selectivity

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remains the same, though the *ees*, 89 and 96 % respectively, are slightly lower. The results of the cyclopropanation in ionic liquids are shown in Table 4.

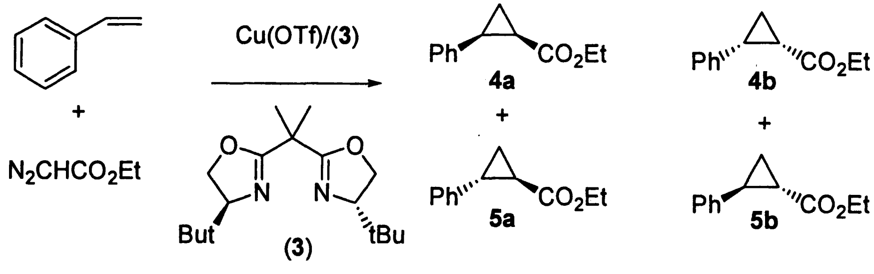

Table 4 Cyclopropanation of styrene with ethyldiazoacetate catalysed by Cu(OTf)/(3) in ionic liquids

Solvent	*Yield /%*[a]	*Selectivity /%* *trans : cis*	*Enantioselectivity /%*[b] *trans : cis*
$CHCl_3$	59	73 : 27	89 : 96
[BMIM][OTf]	53	76 : 24	97 : 95
[BMIM][PF_6]	47	75 : 25	95 : 91
[BMIM][NTf_2]	45	63 : 37	94 : 93
[BMIM][BF_4]	61	75 : 25	95 : 89
[BMIM][BF_4]/[Cl][c]	<1	-	-
[BMIM][BF_4]/[Br][c]	<1	-	-

[a]Determined by GC using decane as an internal standard [b]Determined by chiral GC after conversion to the 1-phenethylamide **5a** was the major *trans* product and **4a** was the major *cis* product [c]Contains 5% [BMIM]X (X = Cl, Br)

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Styrene is not appreciably soluble in the ionic liquids, hence these reactions are biphasic. The reactions were carried out at 10 ^{0}C since some of the ionic liquids are too viscous for efficient magnetic stirring much below this temperature. As can be seen, the yields, regioselectivity and enantioselectivity are similar in all the ionic liquids and in chloroform, though the regioselectivity is somewhat less in the NTf_2 liquid. A previous study found a similar reduction in the regioselectivity in [EMIM][NTf_2] (EMIM = 1-ethyl-3-methylimidazolium) (*23*). However, the yields and enantioselectivities are significantly higher than those (3-50% yield, 0-85% ee) observed previously (*23*) for the same reaction and catalyst.

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A problem that can arise in the use of ionic liquids for immobilisation of transition metal based catalysts is that at low catalyst concentrations impurities in the ionic liquids, particularly halide ions, can have a deleterious effect on the catalysis by coordinating to the metal and blocking an active site as has been noted previously (*26,27*). To investigate this possibility we examined the effect of added [BMIM]X (X = Cl, Br) on the catalysis. Addition of the catalyst to a solution of [BMIM][BF_4] with 5% [BMIM]Cl added gave a homogeneous yellow-green solution whilst if 5% [BMIM]Br was used a deep red/ brown solution was formed. In either case the resultant solution was inactive as a cyclopropanation catalyst though it did lead to decomposition of the ethyl diazoacetate. As we have previously stated, we believe the presence of [EMIM]Br impurity impurity explains the poor results observed previously for copper catalysed cyclopropanation in [EMIM][BF_4] (*23*).

Attempts at recycling and reusing the catalyst were performed in [BMIM][BF_4] since leaching of the catalyst in to the ether used for extracting the products was more of a problem with the more hydrophobic [BMIM][OTf] and [BMIM][NTf_2] and the yield was less in [BMIM][PF_6]. The results are shown in Table 5.

Table 5 Repeated cyclopropanation of styrene with ethyldiazoacetate catalysed by Cu(OTf)/(3) in [BMIM][BF_4]

Run	*Yield /%*[a]	*Selectivity /%*[a] *trans : cis*	*Enantioselectivity /%*[a] *trans : cis*
1	88	75 : 25	97 : 94
2	88	75 : 25	95 : 93
3	90	73 : 27	83 : 91
4	85	72 : 28	98 : 98
5	69	65 : 35	72 : 74
6	71	66 : 34	82 : 86
7	55	69 : 31	87 : 80
8	51	69 : 31	88 : 84

[a] Yield, selectivity and enantioselectivity measured as for Table 4.

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To optimise the yield of cyclopropane we wished to minimise the levels of diethyl maleate and fumarate formed by carbene dimerisation. This was done by decreasing the rate of addition of the ethyl diazoacetate since increasing the concentration of the styrene was not possible due to the limited solubility of styrene in the ionic liquids. The results of performing the reaction eight times in

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the same batch of ionic liquid are displayed in the Table 5. As can be seen for the first four runs the yield and enantioselectivity are comparable. After the fourth run, the yield drops with a slight reduction in selectivity though the enantioselectivity generally remains high.

Asymmetric Diels-Alder Reaction

The Diels-Alder reaction of cyclopentadiene and methacrolein was selected as a model reaction to investigate the effect of the IL anion on the rate and selectivity.

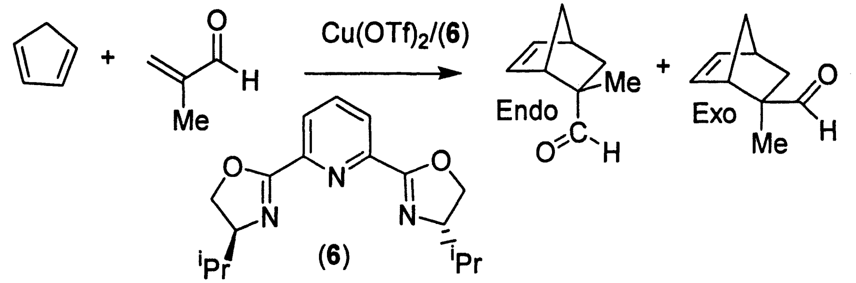

Table 6 Effect of ionic liquid anion on selectivity in the Diels-Alder reaction of methylacrolein and cyclopentadiene catalysed by $Cu(OTf)_2/(6)$

Solvent	*Yield /%*[a]	*Selectivity /% exo : endo*	*Enantioselectivity /%*[b] *exo*
CH_2Cl_2	55	93 : 7	45
[BMIM][OTf]	62	96 : 4	59
[BMIM][PF_6]	68	96 : 4	60
[BMIM][NTf_2]	60	92 : 8	49
[BMIM][BF_4]	66	95 : 5	55

[a]Determined by ^{1}H NMR using ferrocene as an internal standard [b]Determined by ^{1}H NMR after acetalisation with (2*R*, 4*R*)-2,4-penatnediol (*28*).

To assess the impact of low levels of impurities in the ionic liquids we examined the effect of halide or 1-methyimidazole on the reaction. Addition of up to 2 mol% of [BMIM]Cl caused a decrease in yield (from 70 to 22%), selectivity (from *exo*:*endo* 96:4 to 85:15) and enantioselectivity (from 50 to 0%).

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Similar effects were noted on addition of up to 2 mol% of 1-methylimidazole, though the reduction in stereoselectivity was even more marked (*exo*:*endo* 70:30). These findings reflect the need to use high purity ionic liquids that are free from impurities and highlight the fact that both chloride and 1-methylimidazole bind strongly to the copper catalyst. The complexation of 1-methylimidazole with $CuCl_2$ to form $[Cu(1\text{-methylimidazole})_4]^{2+}$ has been described previously as a method of analysis to detect the level of 1-methylimidazole impurity in imidazolium based ionic liquids (*29*). The reaction of cyclopentadiene with other dienophiles was also investigated and the results are shown in Table 7.

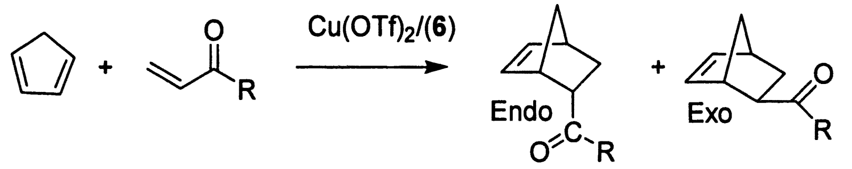

Table 7 Effect of ionic liquid anion on selectivity in Diels-Alder reactions of cyclopentadiene catalysed by $Cu(OTf)_2/(6)$

Solvent		*Yield /%*[a]	*Selectivity /% endo : exo*	*Enantioselectivity /%*[b] *endo*
CH_2Cl_2	H	83	90 : 10	20
[BMIM][OTf]	H	85	91 : 9	25
[BMIM][PF_6]	H	88	91 : 9	28
[BMIM][NTf_2]	H	81	90 : 10	22
[BMIM][BF_4]	H	86	91 : 9	24
CH_2Cl_2	Et	50	91 : 9	34
[BMIM][OTf]	Et	57	90 : 10	36
[BMIM][PF_6]	Et	59	90 : 10	35
[BMIM][NTf_2]	Et	46	90 : 10	33
[BMIM][BF_4]	Et	51	90 : 10	34

[a]Determined by ^1H NMR using ferrocene as an internal standard [b]Determined by ^1H NMR after acetalisation with (2R, 4R)-2,4-penatnediol (*28*).

As can be seen from Table 7 reactions with other substrates are much less enantioselective both in dichloromethane and in the ionic liquids. In general the yields and enantioselectivities are slightly better in the ionic liquids than in

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dichloromethane. There is very little difference between the different ionic liquids though [BMIM]NTf_2 is consistently slightly worse than the others tried.

Overall we have demonstrated that copper oxazoline complexes can catalyse cyclopropanations and Diels-Alder reactions in ionic liquids with comparable yiled and enatioselectivity to conventional solvents. The results were slightly worse in [BMIM][NTf_2] than in the the OTf, PF_6 and BF_4 liquids. Recycling of the catalyst ionic liquid solution is best in the BF_4 or PF_6 liquids since these are more polar and so there is less leaching of the catalyst into the organic solvent used for extraction of the product.

Experimental Section

Diels-Alder Reaction of Methacrolein and Cyclopentadiene in [BMIM]Cl-(x)$ZnCl_2$

Methyl acrylate (360 µl, 4 mmol) was added to [BMIM]Cl-(x)$ZnCl_2$ (x = 0.50) (1.244 g, 4 mmol) and stirred for 5 min to give a homogeneous solution. Freshly cracked cyclopentadiene (282 µl, 4.2 mmol) was added to give a biphasic reaction mixture which was stirred at 25 °C for 64 h. Deionised water (1 ml) was added and the product extracted with diethyl ether (5 x 2ml). A known amount of ferroecene was added as an internal standard and the yield and selectivity were determined by ^{1}H NMR spectroscopy.

General Procedure for Fischer Indole Synthesis

Acetophenone (1.20 g, 10 mmol) and phenyl hydrazine (1.19 g, 11 mmol) were added to [BMIM]Cl-(x)$ZnCl_2$ (x = 0.71) (5.15 g, 10 mmol). The reaction mixture was heated to 100 °C and stirred for 12 h. The product, 2-phenyl indole was sublimed from the ionic liquid.

Procedure for the Pictet Spengler Reaction

Tryptamine (0.160 g, 1 mmol) was added to [BMIM]Cl-(x)$ZnCl_2$ (x = 0.71) (0.103 g, 0.2 mmol) in dichloroethane (2 ml) and benzaldehyde (122 µl, 11.2 mmol) was added. The reaction mixture was stirred at 80 °C for 24 h. After the reaction the ionic liquid had formed a gel, the dichloroethane was decanted and the gel was extracted with more dichloroethane (5 x 2ml). The combined extracts

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were evaporated and the product was separated by preparative tlc. The ionic liquid was dried under vacuum at 80 °C overnight before repeating the reaction.

General Procedure for Copper Catalysed Cyclopropanation

These experiments were carried out as previously reported (*24*).

General Procedure for Copper Catalysed Diels-Alder Reactions

A solution of iPr-pybox (*30*) (**6**) (6.6 mg, 0.022 mmol) in dichloromethane was added to a solution of $Cu(OTf)_2$ (0.022 mmol) in dichloromethane. The blue solution was stirred at room temperature for 3 h, then the ionic liquid (1 ml) was added and the dichloromethane was removed under vacuum. The catalyst solution was then cooled to the reaction temperature and methacrolein (140 mg, 2 mmol) and cyclopentadiene (198 mg, 3 mmol) were added and the reaction was stirred for 16 h. The ionic liquid was then extracted with diethyl ether (5 x 2 ml). The ether washings were passed throough a short plug of silica to remove any catalyst and then evaporated to dryness. The resulting oil was analysed by ^{1}H NMR spectroscopy. The enantioselectivity was determined by conversion to the acetal with (2*R*, 4*R*)-pentanediol and analysis by GC (*28*).

Effect of [BMIM] Cl or methylimidazole on the Diels-Alder reactions

Stock solutions of [BMIM]Cl (18 mg in 0.5 ml CH_2Cl_2) and methylimidazole (24 μl in 1 ml) were prepared. An appropriate amount of the stock solution (5% compared to the ionic liquid) was added to the ionic liquid catalyst solution in dichloromethane. The dichloromethane was then evaporated before addition of the other reagents.

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Chapter 13

Ionic Liquid: A Green Solvent for Organic Transformations I

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Ionic liquids are a class of unconventional solvent having unique chemical and physical properties. The entire molecular framework of ionic liquids is made up of ions. Molten sodium chloride, for example, is an ionic liquid but a solution of sodium chloride in water is an ionic solution. The term molten salts, which were previously used to describe such materials, conjure an image of hot, viscous and highly corrosive medium. The term ionic liquid, in contrast, refers to a material that is fluid at temperature as low as –96 °C, colourless, low viscosity and is easily handled. In patent and academic literature, the term "ionic liquids" now refers to liquids composed entirely of ions that are fluid around or below 100 °C.

Ionic liquids are not new. Some of them have been known for many years. For instance, ethylammonium nitrite, $[EtNH_3][NO_3]$, which has a melting point of 12 °C, was first known in 1914 (1). It was proposed that these ionic liquids provide a useful extension to the range of solvents that are available for synthetic chemistry. However, it was only until recently that the research into ionic liquids intensifies (2). This is mainly due to their favourable properties, such as non-flammability, no measurable vapour pressure, low toxicity, reusability, low cost and high thermal stability. In addition to the polar properties of the ionic liquids, they are non-coordinating, which can avoid any undesired solvent binding in pre-transition states. Ionic liquids have also been referred to as "designer solvent". This is because the polarity and hydrophilicity can be controlled by careful

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selection of cations or anions. Moreover, the ionic liquids can be designed and tuned to optimize yield, selectivity, substrate solubility, product separation, and even enantioselectivity. As a result, ionic liquids are considered to be promising non-conventional solvents for organic reactions. Note that ionic liquids are not intrinsically "green" (some are extremely toxic), but they can be designed to be environmentally friendly, with many potential benefits for sustainable chemistry (3).

Because research into ionic liquids is at an early stage, many of their properties remain to be uncovered. Nevertheless, ionic liquids have been found to be potentially viable solvents for organic synthesis with promising results in many organic reactions, such as hydrogenation (4), hydroformylation (5), Friedel-Crafts acylation (6), Diels-Alder reaction (7), asymmetric allylation reactions (8), asymmetric epoxidation of alkenes (9), and asymmetric ring-opening of epoxides (10). Thus, ionic liquids can be a useful green alternative to replace organic solvents used in organic transformations. Due to their unique properties, we envisage that ionic liquids will provide interesting perspectives of how green chemistry can be integrated into organic chemistry.

In this article, we will provide an up-to-date discussion with regards to the investigations we have done on using ionic liquids in reactions involving the formation of C–C bonds, namely, three-component Mannich-type reaction, direct aldol reaction and Mukaiyama aldol reaction. In the next chapter, we will further discuss our investigation on using ionic liquids in allylation reaction and the synthesis of bis(indolyl)methanes and polyhydroquinoline derivatives.

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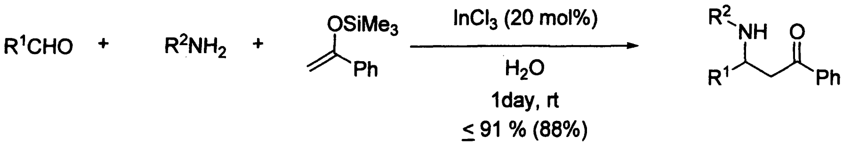
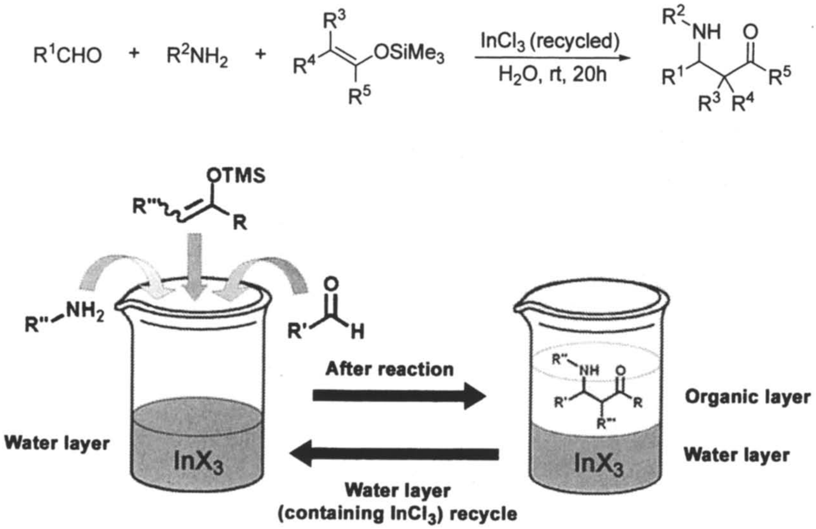
Asymmetric Mannich-Type Reactions Catalyzed by Indium(III) Complexes in Ionic Liquids[1]

In our group's long term focus on environmentally friendly C–C bond forming reactions, we had made a significant contribution in Mannich-type reactions. Using indium trichloride as a catalyst, we have successfully developed a three-component Mannich-type coupling reaction in pure water (12,13). It has been shown that indium trichloride is stable in water and is also able to tolerate the basicity of amines. In fact, apart from catalyzing the reaction, it was also essential for this coupling process to take place in water, without which, only aldimine formation and aldol products were obtained (14). In addition, side reactions commonly associated with the classical Mannich reaction, such as deamination, were not observed. Upon completion of the reaction, the catalyst can be recovered and reused, without significant loss in yields (Scheme *1*).



Scheme 1. Indium trichloride catalyzed Mannich-type reaction in water.

We further applied this methodology to the combinatorial synthesis of *β*-aminocarbonyl compounds (15). By using the recycled indium trichloride as catalyst, we were able to achieve a one-pot Mannich-type reaction smoothly and cleanly with excellent yields (Scheme 2). The recycled indium trichloride can also be used up to 20 times without any significant loss in yield.



Scheme 2. Combinatorial one-pot Mannich-type reaction in water using recycled indium trichloride.

Although the prior discussion demonstrated an environmentally friendly Mannich-type reaction in water, there are some drawbacks to the above method. Most significantly, it is limited to the addition of non-enolizable aldehydes and aromatic amines. This limitation has hindered the development of an asymmetric version of this reaction. We thus directed our studies to investigate the feasibility of an asymmetric Mannich-type reaction in ionic liquids instead of water in our efforts to explore a novel medium and to circumvent the limitation of the reaction in water.

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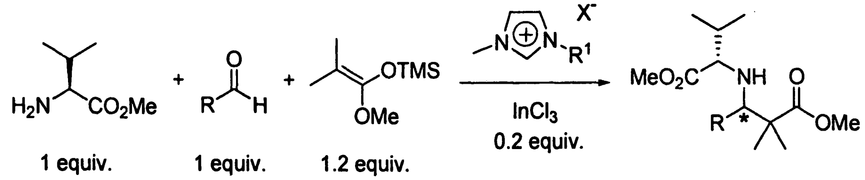
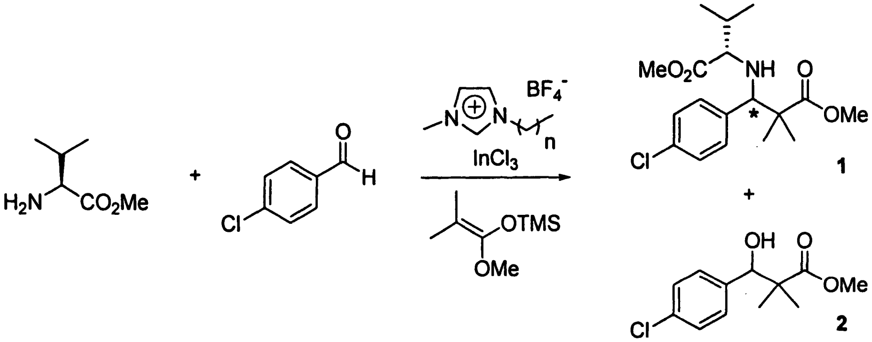
From our previous experience (16,17), L-valine methyl ester was found to be an excellent chiral auxiliary. Thus, it was the chiral auxiliary of choice again in the investigation of the In(III) complex-catalyzed asymmetric Mannich-type reaction (Scheme 3).



Scheme 3. $InCl_3$-catalyzed asymmetric Mannich-type reaction in ionic liquids.

We first investigated the effect of different ionic liquids on the asymmetric Mannich-type reaction using $InCl_3$. Four different ionic liquids were used in this initial study, i.e. butylmethylimidazolium tetrafluoroborate ([bmim]BF_4), hexylmethylimidazolium tetrafluoroborate ([hmim]BF_4), octylmethylimidazolium tetrafluoroborate ([omim]BF_4) and octylmethylimidazolium chloride ([omim]Cl). The results are shown in Table 1.

Table 1. Asymmetric Mannich-type reaction using various ionic liquids.



Ionic Liquid	*Yield*[a]	*Diastereomeric ratio*[b] *(R:S)*	*1:2*
[omim]BF_4, n = 7	50%	92:8	73:27
[hmim]BF_4, n = 5	65%	93:7	93:7
[bmim]BF_4, n = 3	71%	93:7	95:5
[omim]Cl, n = 7	No desired product		

[a] Isolated yield of Mannich product **1**. [b] The diastereomeric ratio of **1** was determined using ^1H and ^{13}C NMR spectroscopy

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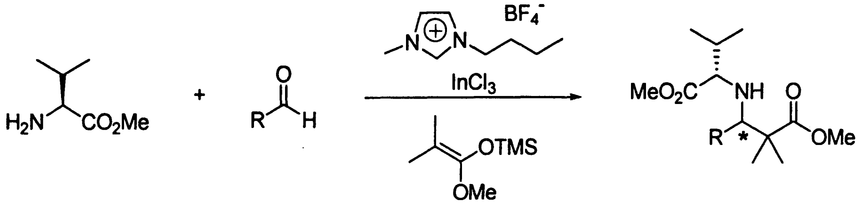
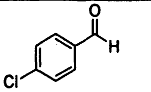
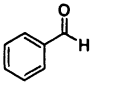
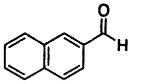
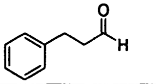
Results showed that this $InCl_3$-catalyzed asymmetric Mannich-type reaction proceeded smoothly in all three BF_4-type ionic liquids but not in [omim]Cl (18). In addition, the diastereoselectivities of the Mannich product **1** were consistently high. However, there was an apparent variability in the ratios of the Mannich product to the aldol side product with an interesting relation to the alkyl chain length of the cationic component of the ionic liquid. The proportion of the Mannich product seems to increase with shortening of the alkyl chain lengths. This result suggests that we can progressively reduce the aldol side product by reducing the hydrophobic chain of the ionic liquid.

We continued our study using $[bmim]BF_4$ with various aldehydes in the presence of $InCl_3$. The yields and diastereomeric ratios are shown in Table 2. In all cases, L-valine methyl ester was found to be a good chiral auxiliary for both aromatic and aliphatic aldehydes. The products were obtained in moderate to good yields with good diastereoselectivities. In contrast to the reaction carried out in water, even enolizable aldimines can be used with this system (Table 2, entry 4).

Table 2. $InCl_3$-catalyzed asymmetric Mannich-type reaction with various aldehydes using $[bmim]BF_4$.



Entry	*Aldehyde*	*Yield*[a]	*Diastereomeric ratio*[b] *(R:S)*
1		71%	93:7
2		86%	91:9
3		74%	90:10
4		50%	93:7

[a] Isolated yield of Mannich product **1**. [b] The diastereomeric ratio of **1** was determined using ^1H and ^{13}C NMR spectroscopy.

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The excellent diastereoselectivities observed may be explained using the transition state model as shown in Figure 1. In this model, the carbonyl oxygen and the α-nitrogen of the ester moiety chelates to the $InCl_3$ to form a rigid bidentate transition state. The bulky isopropyl group of the L-valine methyl ester selectively shields the *Re* face, leaving the *Si* face available for attack, thereby rendering the nucleophilic addition process a highly diastereoselective one. As a result, the (*R*,*S*)-diastereomer is the major product in all cases.

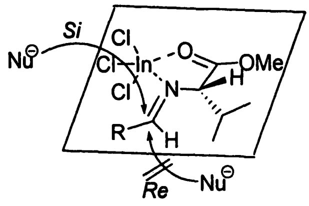

Figure 1. Transition state model of highly diastereoselective Mannich-type reaction.

Our attempts to recycle and reuse the ionic liquids in the same reaction failed to afford the desired Mannich product. However, addition of a further 0.2 equivalent of $InCl_3$ to the recycled [hmim]BF_4 allowed the asymmetric Mannich-type reaction to proceed in 50% yield and 82% de with 4-chlorobenzaldehyde. This less than satisfactory result prompted us to look for a more useful catalyst which can be recycled and reused after the reaction together with the ionic liquid as a system.

From our previous experience, $In(OTf)_3$ could be recycled and reused without any significant decrease in its catalytic performance. Therefore, it was envisaged that this In(III) complex could be employed in the three-component asymmetric Mannich-type reaction in ionic liquids. Our study with various aldehydes shows that this is indeed feasible (Table 3).

Having this excellent result in hand, we proceeded to investigate the reusability of $In(OTf)_3$ as before. The process was investigated (Table 4) starting with fresh [hmim]BF_4 and $In(OTf)_3$ with 4-chlorobenzaldehyde. After the reaction was completed (monitored by TLC), the ionic liquid together with the $In(OTf)_3$ were recycled and reused in the next reaction involving the same aldehyde. The yields and selectivities were found to be comparable to the fresh ionic liquid and catalyst. Interestingly, a switch in the third cycle using benzaldehyde instead of 4-chlorobenzaldehyde resulted in a decrease in yield to only 13% and the selectivity was found to be only 76% de. The cause of this decrease in performance is still under investigation.

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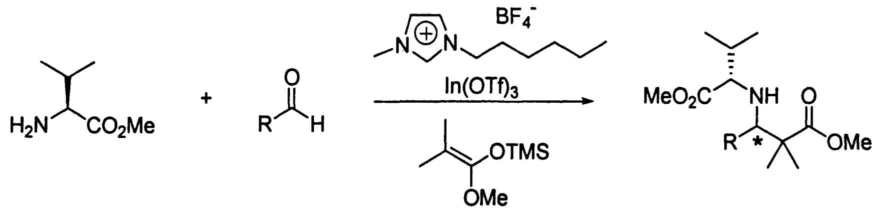
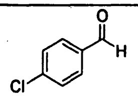
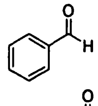
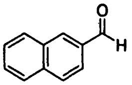
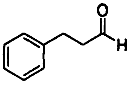
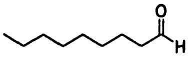
Table 3. In(OTf)$_3$-catalyzed asymmetric Mannich-type reaction with various aldehydes using [hmim]BF_4.



Entry	*Aldehyde*	*Yield*[a]	*Diastereomeric ratio*[b] *(R:S)*
1		65%	93:7
2		51%	91:9
3		61%	89:11
4		50%	80:20
5		53%	82:18

[a] Isolated yield of Mannich product 1. [b] The diastereomeric ratio of 1 was determined using ^{1}H and ^{13}C NMR spectroscopy.

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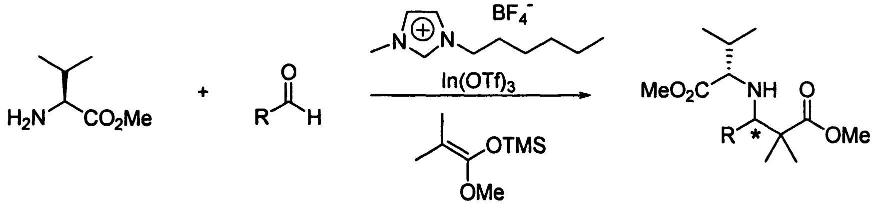
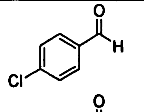
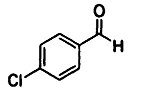
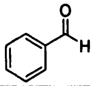
Table 4. Investigation on the asymmetric Mannich-type reaction in $[hmim]BF_4$ using recycled $In(OTf)_3$.



Entry[a]	*Cycle*	*Aldehyde*	*Yield*[b]	*Diastereomeric ratio*[c] *(R:S)*
1	1st cycle		65%	93:7
2	2nd cycle		65%	92:8
3	3rd cycle		13%	88:12

[a] For each entry, <5% of aldol product was observed.[b] Isolated yield of the Mannich product. [c] The diastereomeric ratio was determined using ^1H and ^{13}C NMR spectroscopy.

To sum up, we have successfully developed a highly diastereoselective Mannich-type reaction catalyzed by $InCl_3$ or $In(OTf)_3$ using ionic liquids. This reaction proceeded smoothly with a wide variety of aldehydes at room temperature, and gave high diastereoselectivities and yields. With these results, we continue to investigate the feasibility of using ionic liquids in various other organic transformations.

L-Proline Catalyzed Asymmetric Direct Aldol Reactions in Ionic Liquids (19)

Our group has reported the first investigation of the asymmetric direct aldol reaction in ionic liquids (Scheme 4). In this work, the catalytic activity of L-proline in imidazolium-based ionic liquids, and the capacity of such a system to be reused, was studied.

From the literature (20), 60% ee was obtained for the L-proline catalyzed direct aldol reaction using benzaldehyde and acetone in DMSO. Instead of

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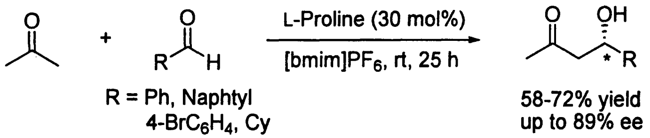
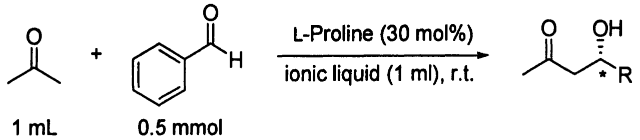


Scheme 4. L-Proline in an ionic liquid as an efficient and reusable catalyst for asymmetric direct aldol reactions.

DMSO, we decided to try this direct aldol reaction with various types of imidazolium-based ionic liquids. The results are summarized in Table 5. Using 0.5 mmol of benzaldehyde, 1 ml of acetone and 30 mol% of L-proline in 1 ml of ionic liquid, we found that the reaction went smoothly with these imidazolium-based ionic liquids. Most importantly, these ionic liquids gave the desired aldol product with similar or better enantioselectivities as compare to the use of DMSO as a solvent (20). Furthermore, we found that the reaction carried out in [omim]Cl (Table 5, entry 2) proceeded faster than that in other ionic liquids. A 100% conversion was observed on TLC after 20 hours with a subsequent purified yield of 78%. However, significant side products were observed from the elimination of water at an early part of the reaction. This is unlike the [bmim]PF_6 system in which the elimination product only bears significance after 45 hours (Table 5, entry 5) and gave the desired aldol product after 20 hours (Table 5, entry 4).

Table 5. L-Proline-catalyzed asymmetric direct aldol reaction of acetone and benzaldehyde in various ionic liquids.



Entry	*Ionic Liquid*	*Time (hour)*	*ST:EP:AP*[a]	*Yield*	*ee*[b]
1	[hmim]BF_4	45	6:34:60	50%	58%
2	[omim]Cl	20	0:55:45	30%	78%
3	[omim]BF_4	20	11:16:73	59%	71%
4[c]	[bmim]PF_6	20	40:0:60	48%	71%
5	[bmim]PF_6	45	13:12:75	65%	71%
6[d]	[bmim]PF_6	45	34:7:59	43%	65%

[a] ST = starting material (benzaldehyde); EP = elimination product; AP = aldol product. Relative ratio was estimated based on crude NMR. [b] The ee was determined by chiral HPLC using a Chiralcel OB column. [c] No elimination product was detected by ^{1}H NMR. [d] This reaction was carried out using 5 mol% L-proline and 10 equivalents of acetone.

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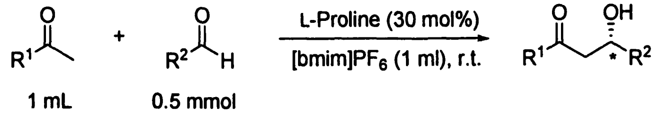
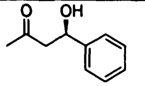
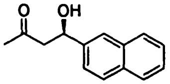
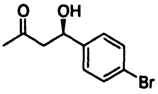
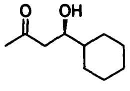
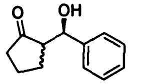
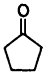
We next reduced the catalyst loading to 5 mol% L-proline and the acetone to 10 equivalents (with respect to benzaldehyde) and conducted the reaction in [bmim]PF_6 (Table 5, entry 6). After 48 hours, the desired aldol product was isolated in 43% yield with 65% ee. Thus, reduced catalyst loading affected the yield but not the ee value.

After considering both the yield and enantioselectivity of the reaction, [bmim]PF_6 was chosen as the reaction media for further investigation with various types of aromatic and aliphatic aldehydes (Table 6). In all cases, the expected aldol products were obtained in good yields with moderate to excellent enantioselectivities. Besides acetone, cyclopentanone was also studied and an excellent yield together with good diastereoselectivity was observed (Table 6, entry 5).

Table 6. L-Proline catalyzed asymmetric direct aldol reactions in [bmim]PF_6.



Entry	*Products*	*R¹*	*R²*	*Time (hour)*	*ST:EP:AP*[a]	*Yield*	*ee*[b]
1		Me	Ph	25	13:12:75	58%	71%
2		Me	Naphtyl	25	15:14:71	60%	69%
3		Me	*p*-BrPh	25	6:8:86	72%	67%
4		Me	*c*-C_6H_{11}	25	8:11:81	65%	89%
5			Ph	25	5:0:95	83% (*dr* = *61:39*)[c]	nd[d]

[a] ST = starting material (aldehyde); EP = elimination product; AP = aldol product. Relative ratio was estimated based on crude NMR. [b] The ee was determined by chiral HPLC using a Chiralcel OB column or Chiralpak AD column. [c] Relative stereochemistry not determined. [d] nd = not determined, since the two diastereoisomers cannot be separated by flash column chromatography, we were unable to analyze the ee.

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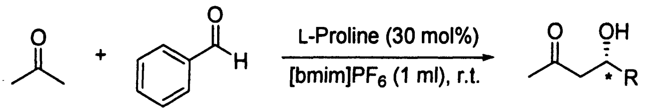
We continued our study by exploring the reusability of L-proline using acetone and benzaldehyde in [bmim]PF_6 as our model system. After the reaction, the ionic liquid containing the L-proline was recycled and reused (Table 7). It was found that the desired aldol product was obtained with comparable yield and enantioselectivity even after four cycles.

Table 7. Recycling study of the L-proline-catalyzed direct asymmetric aldol reaction.



1 mL 0.5 mmol

Entry	*Cycle*	*ST:EP:AP*[a]	*Yield*	*ee*[b]
1	1st Cycle	13:12:75	58%	71%
2	2nd Cycle	19:10:71	56%	71%
3	3rd Cycle	17:16:67	53%	69%
4	4th Cycle	11:23:66	52%	67%

[a] ST = starting material (benzaldehyde); EP = elimination product; AP = aldol product. Relative ratio was estimated based on crude NMR. [b] The ee was determined by chiral HPLC using a Chiralcel OB column.

In summary, the asymmetric direct aldol reaction catalyzed by L-proline has been successfully carried out in imidazolium-based ionic liquids with similar or better ee values as compared to the results carry out using DMSO. The ionic liquid together with the L-proline can be recycled and reused for at least four cycles without any drop in activity. This method has once again demonstrated the possibility of carrying out the asymmetric reactions in ionic liquids which greatly enhances the synthetic value of ionic liquids as green organic reaction media.

Mukaiyama Aldol Reaction in Ionic Liquids (21)

Mukaiyama aldol reaction is one of the most important C–C bond formations in organic synthesis (22,23). Although the Mukaiyama aldol reaction has been extensively studied, to carry out the reaction at ambient temperature in the absence of Lewis acid catalysis or any special activation poses a challenge for organic chemists (24).

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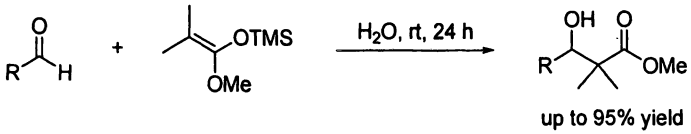
Recently, our group had developed a water-accelerated Mukaiyama aldol reaction using ketene silyl acetals (Scheme 5) (20d). Using this method, Mukaiyama aldol reactions can proceed in water at room temperature without any Lewis acid or special activation to afford the corresponding aldol products in moderate to good yields. However, this reaction only works with reactive aldehydes. No reaction was observed with aliphatic aldehydes. Therefore, a more general method that could work with a wide variety of aldehydes is desirable.



Scheme 5. Water-accelerated Mukaiyama aldol reaction.

In the previously mentioned studies of the asymmetric Mannich-type reaction in 1-*R*-3-methylimidazolium based ionic liquids (25), the Mukaiyama aldol product, as compared to the Mannich product, increased with increasing carbon chain length of the ionic liquids. These findings, coupled with the unique nature of ionic liquids, encouraged us to investigate further the effects of ionic liquids in Mukaiyama aldol reactions.

We first began with the investigation of the Mukaiyama aldol reaction of nonyl aldehyde and 1-methoxy-2-methyl-1-trimethylsilyloxypropene in different ionic liquids. The results are shown in Table 8. As predicted, the ionic liquids with longer carbon chain lengths of the cation gave better yields of the aldol products (Table 8, entries 3, 5 and 7). In addition, the Cl-type ionic liquids were the preferred solvent systems (Table 8, entries 6 and 7) for this Mukaiyama aldol reaction as higher yields were obtained as compared to other types of ionic liquids.

Next, we investigated the Mukaiyama aldol reaction of 1-methoxy-2-methyl-1-trimethylsilyloxypropene with various aldehydes using [omim]Cl (n=7). The results are shown in Table 9. In all cases, the products were obtained in moderate to good yields. Note that even unreactive aliphatic aldehydes (Table 9, entries 1, 2 and 8) and aromatic aldehydes (Table 9, entries 7, 9, 10 and 11) reacted with the 1-methoxy-2-methyl-1-trimethylsilyloxypropene in this system to yield appreciable products.

A wide-ranging Mukaiyama aldol reaction using ionic liquids as solvents at room temperature in the absence of Lewis acid or other promoter has thus been developed. This method is applicable to various classes of aldehydes. However, further improvements in the moderate to good yields (50 to 74%) are still necessary through design of new ionic liquids that improve the effectiveness of the Mukaiyama aldol reaction.

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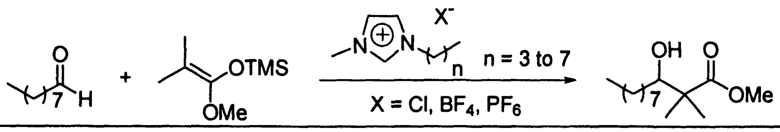
Table 8. Investigation of Mukaiyama aldol reaction using various ionic liquids.



Entry	*Ionic Liquid*	*Yield*[a]
1	[bmim]PF_6, n = 3	4%
2	[hmim]PF_6, n = 5	6%
3	[omim]PF_6, n = 7	12%
4	[bmim]BF_4, n = 3	8%
5	[hmim]BF_4, n = 5	29%
6	[hmim]Cl, n = 5	50%
7	[omim]Cl, n = 7	51%

a. Isolated yield of aldol product.

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Conclusion

Using ionic liquids, we have successfully developed simple and useful methodologies for asymmetric Mannich-type reactions, L-proline-catalyzed direct aldol reactions and Mukaiyama aldol reactions. In next chapter, we would further explore the potential of using ionic liquids in organic synthesis. We believe that the simplicities of all these methods have provided easy access and effective pathways to synthesize synthetically useful organic compounds.

Acknowledgement

We thank the Nanyang Technological University and the National University of Singapore for their generous financial support. We would also like to acknowledge the hard work, perseverance, and insight of the graduate students that made this review possible.

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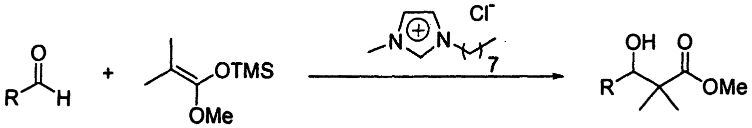
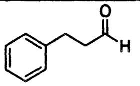
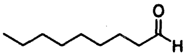
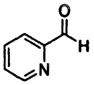
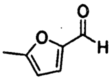
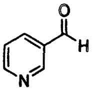
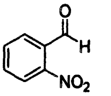
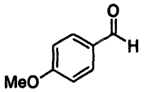
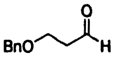
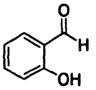
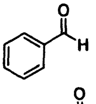
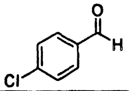
Table 9. Mukaiyama aldol reaction using [omim]Cl with various aldehydes.



Entry	*Aldehyde*	*Yield*[a]
1		50%
2		51%
3		53%[b]
4		58%
5		59%[b]
6		60%
7		62%
8		63%
9		68%
10		72%
11		74%

[a] Isolated yield of aldol product. [b] Including TMS protected aldol product.

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Chapter 14

Ionic Liquid: A Green Solvent for Organic Transformations II

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Recently, the research into ionic liquids was blooming (1). This is mainly due to the favourable properties of ionic liquids, such as non-flammability, no measurable vapour pressure, low toxicity, reusability, low cost and high thermal stability. In addition to the polar properties of the ionic liquids, they are non-coordinating, which can avoid any undesired solvent binding in pre-transition states. Due to their unique properties, we envisage that ionic liquids will provide interesting perspectives of how green chemistry can be integrated into organic chemistry.

In this article, we will continue our previous discussion and provide the details of current investigations we have done on using ionic liquids in reactions involving allylation reaction and the synthesis of bis(indolyl)methanes and polyhydroquinoline derivatives.

$InCl_3$-Promoted Allylation of Aldehydes in Ionic Liquids (2)

Allylation reactions of various carbonyl compounds are valuable C–C bond forming reactions for the preparation of synthetically useful homoallylic alcohols (2). Although Lewis acid or Brønsted acid catalyzed allylation reactions in aqueous media with allytributyltin have been reported (2,3,4), more active and efficient catalytic systems are still highly sought-after. Recently, our group had

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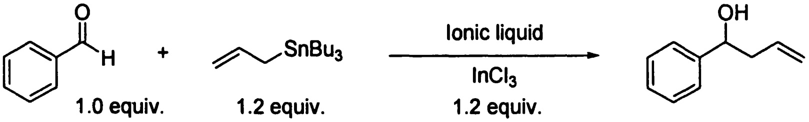
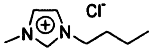
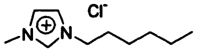
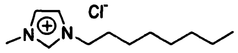
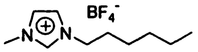
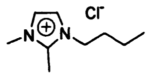
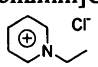
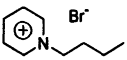
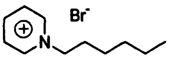
In Ionic Liquids in Organic Synthesis; Malhotra, S.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2007.

investigated the $InCl_3$-promoted allylation reactions of aldehydes using allyltributyltin in ionic liquids.

We first carried out our study on the $InCl_3$-promoted allylation using benzaldehyde and allyltributyltin in various different type of ionic liquids. The results are summarized in Table 1. It was found that the allylation reactions went smoothly with moderate to good yields (60% to 80%). Among them, [hmim]Cl and [omim]Cl gave us the best results (80% and 82% respectively).

Table 1. $InCl_3$-promoted allylation of benzaldehyde in various types of ionic liquids



Entry	*Ionic Liquid*	*Temp (°C)*	*Time (hour)*	*Yield*[a]
1	 [bmim]Cl	40	16	70%
2	 [hmim]Cl	25	16	80%
3	 [omim]Cl	25	14	82%
4	 [hmim]BF_4	25	12	75%
5	 [bmmim]Cl	55	16	68%
6	 [epy]Cl	60	16	66%
7	 [bpy]Br	45	14	60%
8	 [hpy]Br	40	14	62%

[a] Isolated yield.

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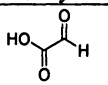
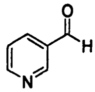
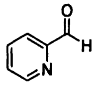
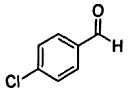
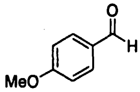
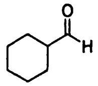
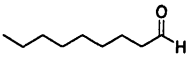
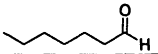
We then directed our studies to investigate the allylation reaction with various aldehydes in the presence of $InCl_3$ in hexylmethylimidazolium chloride, [hmim]Cl. The results are shown in Table 2. In all cases, $InCl_3$ proved to be an efficient promoter for both aromatic and aliphatic aldehydes to afford the desired products in moderate to high yields.

Table 2. $InCl_3$-promoted allylation reaction with various aldehydes using [hmim]Cl.

1.0 equiv.   1.2 equiv.   1.2 equiv.

Entry	*Aldehyde*	*Time (hour)*	*Yield*[a]
1		8	93%
2		14	88%
3		14	86%
4		16	82%
5		16	78%
6		18	76%
7		20	73%
8		20	72%

[a] Isolated yield of allylation product. All of the products were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy

Efforts were made to recycle and reuse the ionic liquid and catalyst. This process was investigated starting with fresh [hmim]Cl and 4-chlorobenzaldehyde in the presence of $InCl_3$ (Table 3). After the reaction, the ionic liquid, together

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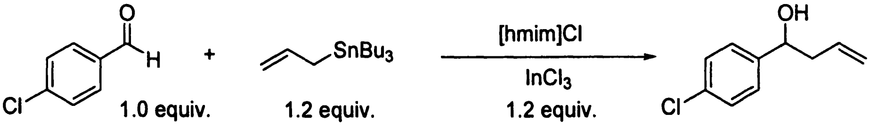
with the $InCl_3$, was recycled and reused for the second cycle. Unfortunately, no desired product was obtained (Table 3, entry 2). This could be due to the transmetallation of tin with $InCl_3$. Thus, 1 equivalent of $InCl_3$ was required to be added to the recycled ionic liquid at every cycle to allow the allylation reaction to proceed in good yields (Table 3, entries 3, 4 and 5).

Table 3. Recycling study on the allylation reaction in [hmim]Cl.



Entry	*Cycle*	*Yield*[a]
1	1[st] cycle	86%
2	2[nd] cycle[b]	0%
3	3[rd] cycle	80%
4	4[th] cycle	76%
5	5[th] cycle	66%

[a] Isolated yield of allylation product. [b] Without addition of $InCl_3$.

We also investigated the asymmetric version of allylation reaction in ionic liquids by adding different types of chiral ligands. We screened through some of the chiral ligands, as shown in Figure 1, with 4-chlorobenzaldehyde in [hmim]Cl. Among them, (*S*)-2-(diphenylmethanol)-1-(2-pyridylmethyl) pyrrolidine 7 gave the best enantioselectivity.

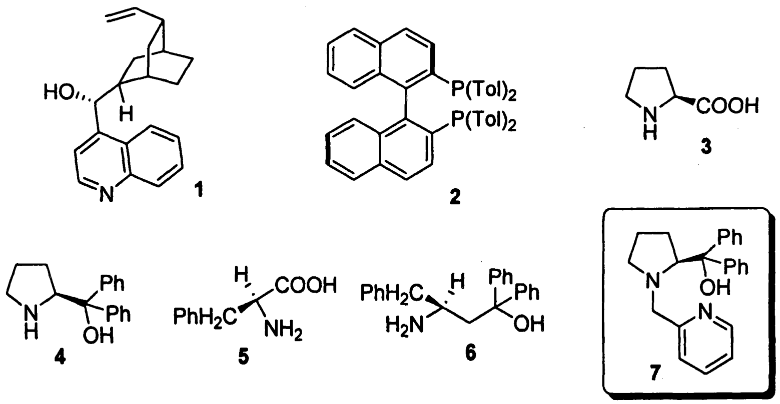


Figure 1. Chiral ligands.

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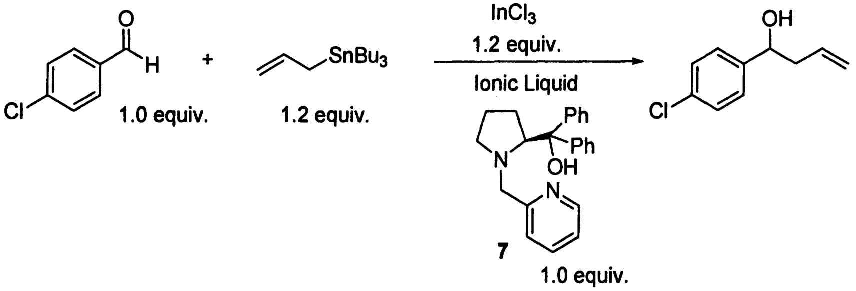
We then proceeded to use 7 and examined a series of ionic liquids in the asymmetric allylation reaction. The results are summarized in Table 4. The allylation proceeded smoothly in these six ionic liquids with low to moderate enantioselectivities (16% to 48% ee), and the reaction carried out in [hmim]Cl gave the best result (Table 4, entry 2, 88% yield, 48% ee).

The reaction of various aldehydes in [hmim]Cl and 7 as the chiral ligand was subsequently studied and good to moderate yields were obtained. The results are shown in Table 5. The aromatic aldehydes gave the desired product

Table 4. Enantioselective allylation of 4-chrolobenzaldehye using (*S*)-2-(diphenylmethanol)-1-(2-pyridylmethyl) pyrrolidine 7 in various ionic liquids.



Entry	*Ionic Liquid*	*Temp (°C)*	*Yield*[a]	*ee*[b]
1	[bmim]Cl	35	86%	39%
2	[hmim]Cl	25	88%	48%
3	[bmmim]Cl	65	84%	16%
4	[hmim]BF_4	25	78%	26%
5	[bpy]Br	40	82%	21%
6	[hpy]Br	35	80%	38%

[a] Isolated yield. [b] The enantioselectivities were determined using HPLC analysis of the ester from *O*-methyl- (*S*)-mandelic acid.

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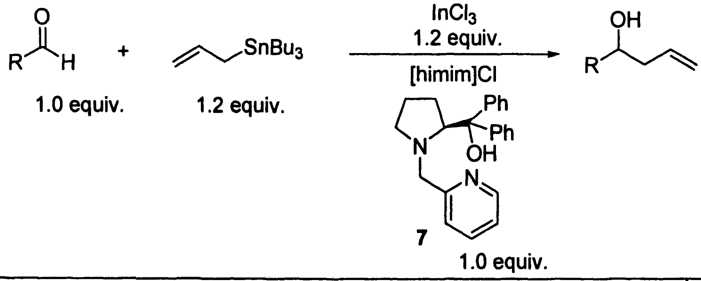
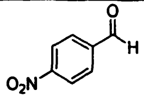
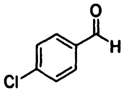
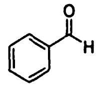
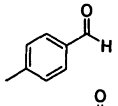
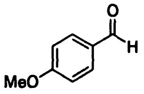
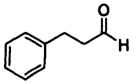
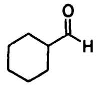
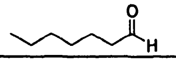
Table 5. Enantioselective allylation of aldehyde catalyzed by (*S*)-2-(diphenylmethanol)-1-(2-pyridylmethyl) pyrrolidine 7 in [hmim]Cl.



Entry	*Aldehyde*	*Yield*[a]	*ee*[b,c]
1		89%	56% (*R*)
2		88%	48% (*R*)
3		88%	46% (*R*)
4		88%	42% (*R*)
5		85%	39% (*R*)
6		81%	10% (*S*)
7		79%	12% (*R*)
8		76%	8% (*R*)

[a] Isolated yield. [b] The enantioselectivity was determined by ^{1}H NMR analysis of the ester from *O*-methyl-(*S*)-mandelic acid. [c] The absolute configuration was determined by comparing with the literature values of optical rotations (7).

with moderate enantioselectivities (Table 5, entries 1, 2, 3, 4 and 5) while the aliphatic aldehydes gave low ee values (Table 5, entries 6, 7 and 8).

In conclusion, we had explored the $InCl_3$-promoted allylation reaction in ionic liquids. The first study on the asymmetric allylation in ionic liquids was also reported. Although only moderate enantioselectivities were obtained, these results served as starting points for our future research.

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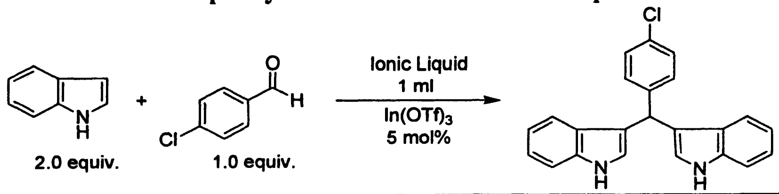
Lewis Acid-Catalyzed Synthesis of Bis(indolyl)methanes in Ionic Liquids (8,9)

The biologically active indoles and their derivatives have long been of interest as pharmaceuticals (10). Bisindolylalkanes and their derivatives have received more attention because of their existence as bioactive metabolites of terrestrial and marine origin (11). The simple method for the synthesis of this class of compounds involves the electrophilic substitution of indoles with various aldehydes and ketones in the presence of either protic (12) or Lewis acids (13,14). However, more than stoichiometric amounts of Lewis acids are required due to deactivation of the catalyst by the basic nitrogen (15). Recently, $LiClO_4$ (16), $In(OTf)_3$ (17) and I_2 (18) were found to catalyze this reaction. Although these catalysts are very useful and efficient, the long reaction time (4 to 10 hours), complicated manipulation, along with the use of organic solvents with their poor recovery and reusability, limited their development from the viewpoint of green chemistry. Hence, we decided to investigate the synthesis of bis(indolyl)methanes in ionic liquids catalyzed by an appropriate Lewis acid.

First, we studied the effect of different ionic liquids on this reaction using $In(OTf)_3$. Six different systems using [bmim]BF_4, [bmim]PF_6, [hmim]PF_6, [omim]PF_6, [dmim]PF_6 and [hmim]Cl were employed in our investigation. The results are shown in Table 6. It was found that in BF_4 and PF_6 type ionic liquids, the electrophilic substitution reactions of indoles with 4-chlorobenzaldehyde proceeded smoothly with high yields. However, no desired products were obtained when using [hmim]Cl (Table 6, entry 6).

We then examined the catalytic activity of different Lewis acids in [omim]PF_6 and the results are as shown in Table 7 . The reaction proceeded

Table 6. $In(OTf)_3$-catalyzed synthesis of 3,3'-bis(indolyl)-4-chlorophenylmethane in various ionic liquids



Entry	*Ionic Liquid*	*Time (min)*	*Yield*[a]
1	[bmim]PF_6	15	89%
2	[hmim]PF_6	15	95%
3	[omim]PF_6	15	96%
4	[dmim]PF_6	60	82%
5	[bmim]BF_4	15	81%
6	[hmim]Cl	720	0%

[a] Isolated yield.

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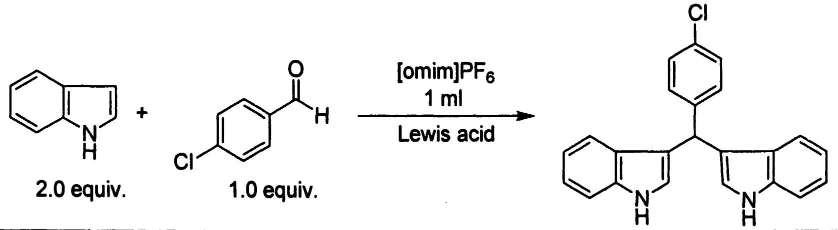
smoothly with all the investigated catalysts. Among them, $In(OTf)_3$ showed the highest catalytic activity as the reaction was completed in 15 mins (Table 7, entry 1). We also found that when a weaker Lewis acids such as $ZnCl_2$ (Table 7, entry 4) was utilized, longer reaction times were required.

Table 7. Synthesis of 3,3'-bis(indolyl)-4-chlorophenylmethane using different Lewis acids in [omim]PF_6.



Entry	*Lewis acid (mol%)*	*Time (hour)*	*Yield*[a]
1	$In(OTf)_3$ (5)	0.25	96%
2	$BiCl_3$ (10)	1.5	93%
3	$YbCl_3$ (5)	4	87%
4	$ZnCl_2$ (10)	7	79%
5	$InCl_3$ (10)	1	71%

[a] Isolated yield.

The reactivities of various aldehydes were then investigated with the optimized $In(OTf)_3$ in [omim]PF_6 system. The results are shown in Table 8. Overall, the reaction proceeded with both aromatic and aliphatic aldehydes with good to excellent yields.

We then continued our study on the reusability of the $In(OTf)_3$ in [omim]PF_6. We found that the catalytic activity of $In(OTf)_3$ gradually decreased in the second and third cycles (Table 10). In the fourth cycle, we did not observe any desired product. However, following the addition of another 5 mol% of $In(OTf)_3$ to the recycled [omim]PF_6, the reaction proceeded with the same efficiency as fresh ionic liquid.

Although we have developed an efficient $In(OTf)_3$-catalyzed electrophilic substitution reaction of indoles with various aldehydes to synthesize the bis(indolyl)methanes, the deactivation of $In(OTf)_3$ was observed during the recycling process. As a result, it is essential for us to continue our study to develop a more practical and efficient catalytic systems.

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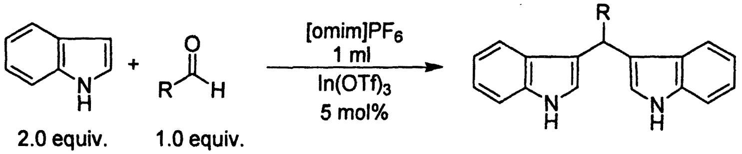
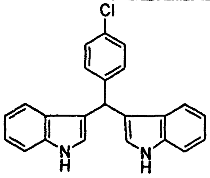
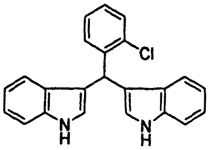
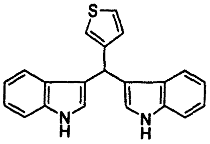
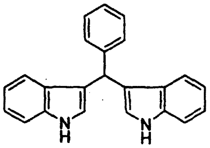
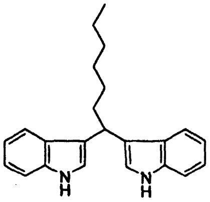
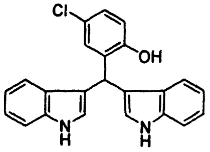
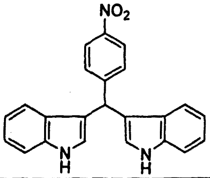
Table 8. In(OTf)$_3$-catalyzed synthesis of bis(indolyl)methanes with various aldehydes using [omim]PF$_6$.



2.0 equiv. 1.0 equiv.

Entry	*Product*[a]	*Time (min)*	*Yield*[b]
1		15	96%
2		30	95%
3		15	92%
4		15	90%
5		15	89%
6		75	86%
7		70	78%

Continued on next page.

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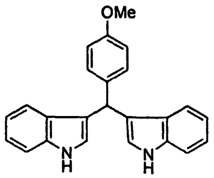
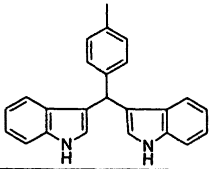
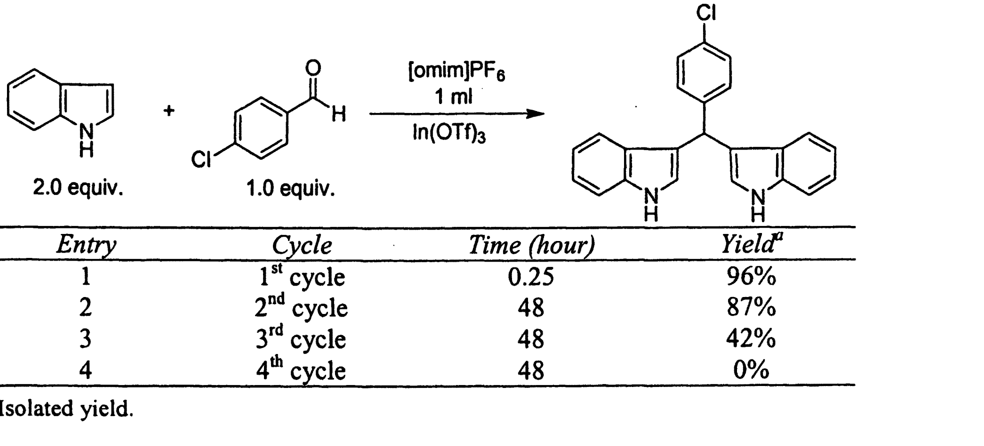
Table 8. *Continued*

Entry	*Product*[a]	*Time (min)*	*Yield*[b]
8		15	76%
9		20	73%

[a] All products were characterized by ^1H NMR, IR and HRMS spectra. [b] Isolated yield.

Table 9. Synthesis of 3,3'-bis(indolyl)-4-chlorophenylmethane using recycled [omim]PF_6 with In(OTf)$_3$.



Entry	*Cycle*	*Time (hour)*	*Yield*[a]
1	1st cycle	0.25	96%
2	2nd cycle	48	87%
3	3rd cycle	48	42%
4	4th cycle	48	0%

[a] Isolated yield.

Fe(III) salts are well known to catalyze many organic transformations, including oxidation of sulfides (19), Michael reaction (20), thia-Fries rearrangement (21) and the synthesis of 1,6-anhydroglucopyraboses (22). Recently, Suranna *et al.* reported the Michael addition of acetylacetone and methyl vinyl ketone in ionic liquids catalyzed by several metal complexes (23), including $FeCl_3 \cdot 6H_2O$. They found that the catalytic activity was strongly dependent on the presence of halide impurities of the ionic liquids. In view of the excellent properties of Fe(III) salts such as commercial availability, ease of handling and low toxicity, we decided to investigate the synthesis of bis(indolyl)methanes using Fe(III) salts as the catalyst.

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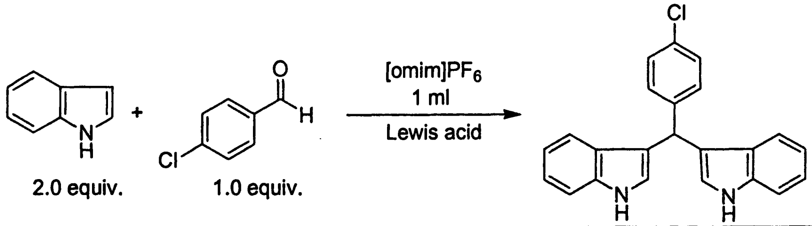
We screened through a series of Fe(III) salt for the condensation reaction of indoles and 4-chlorobenzaldehyde using [omim]PF_6. The results are summarized in Table . We found that 96% yield was obtained while using $FeCl_3 \cdot 6H_2O$ as the catalyst (Table , entry1). The activity of $FeCl_3 \cdot 6H_2O$ was shown to be as good as the activity of $In(OTf)_3$ (Table , entry 9). Using $Fe(NO_3)_3 \cdot 9H_2O$ as a catalyst, the reaction proceeded slowly and, after 48 hours, 95% yield was obtained. However, when changing the catalyst to $Fe_2(SO_4)_3 \cdot xH_2O$, the condensation reaction did not proceed (Table , entry 3). We also tested on the catalytic activities of other different transition metal chlorides, such as $CoCl_2 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$, $CuCl_2 \cdot 6H_2O$, $SmCl_3 \cdot 5H_2O$ and LiCl (Table , entry 4 to entry 8). Among them, only $CoCl_2 \cdot 6H_2O$ is able to promote the condensation reaction and give us the desired product in 55% yield (Table , entry 4).

Table 10. The condensation reaction of indole and 4-chlorobenzaldehyde in [omim]PF_6 with various Lewis acids.



Entry	*Lewis acid (mol%)*	*Time (hour)*	*Yield*[a]
1	$FeCl_3 \cdot 6H_2O$ (5)	0.5	96%
2	$Fe(NO_3)_3 \cdot 9H_2O$ (5)	6.5	95%
3	$Fe_2(SO_4)_3 \cdot xH_2O$ (5)	48	0%
4	$CoCl_2 \cdot 6H_2O$ (5)	48	55%
5	$NiCl_2 \cdot 6H_2O$ (5)	48	0%
6	$CuCl_2 \cdot 6H_2O$ (5)	48	0%
7	$SmCl_3 \cdot 5H_2O$ (5)	48	0%
8	LiCl (10)	48	0%
9	$In(OTf)_3$ (5)	0.25	96%

[a] Isolated yield.

With the above information, we continued our study on the reusability of the [omim]PF_6/$FeCl_3 \cdot 6H_2O$ system. In Table , we compared the yields of the condensation reaction using the recycled [omim]PF_6 with two different catalysts, $In(OTf)_3$ and $FeCl_3 \cdot 6H_2O$, and it was found that [omim]PF_6/$FeCl_3 \cdot 6H_2O$ can be easily recycled and reused for the condensation reaction up to at least 4 cycle with good yields.

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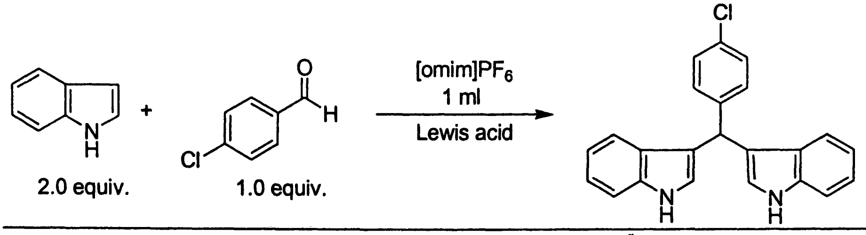
Table 11. The condensation reaction using recycled $[omim]PF_6/In(OTf)_3$ and $[omim]PF_6/FeCl_3{\cdot}6H_2O$.



Entry	Catalytic System	Yield[a] (time) 1st cycle	2nd cycle	3rd cycle	4th cycle
1	$[omim]PF_6/ FeCl_3{\cdot}6H_2O$	96% (0.5 h)	91% (3 h)	91% (23 h)	87% (24 h)
2	$[omim]PF_6/In(OTf)_3$	96% (0.5 h)	87% (48 h)	42% (48 h)	0% (48 h)

[a] Isolated yield.

In short, we reported the first Fe(III)-catalyzed condensation reaction of indoles and aldehydes. It is noteworthy that the $FeCl_3{\cdot}H_2O/[omim]PF_6$ catalytic system can be recycled and reused up to four cycles without any significant loss of activity.

Ionic Liquids-Promoted One-Pot Synthesis of Polyhydroquinoline Derivatives under Solvent Free Conditions(24)

Recently, much attention has been directed towards the synthesis of 1,4-dihydro pyridyl compounds. This is mainly due to their biological activities (25-30). This group of compounds are known as the "chain-cutting agent" of factor IV channel (25-28) which can cure the disordered heart ratio (29,30). As a result, many methods were reported for the synthesis of these polyhydroquinoline derivatives.[i] However, most of them require long reaction times, harsh reaction conditions and large amount of organic solvent. Therefore, simpler methods to synthesize this useful polyhydroquinoline are sought after.

To continue our previous work, we developed a four-component synthesis of polyhydroquinoline derivatives in the presence of a catalytic amount of ionic liquids under solvent free condition (*Scheme 1*).

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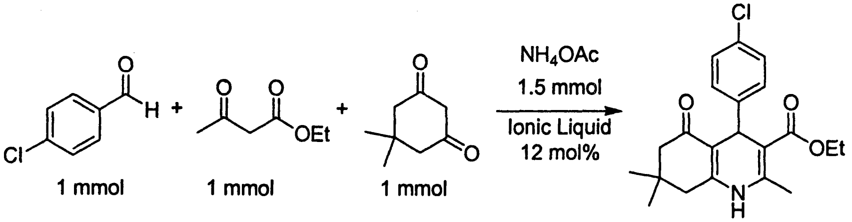
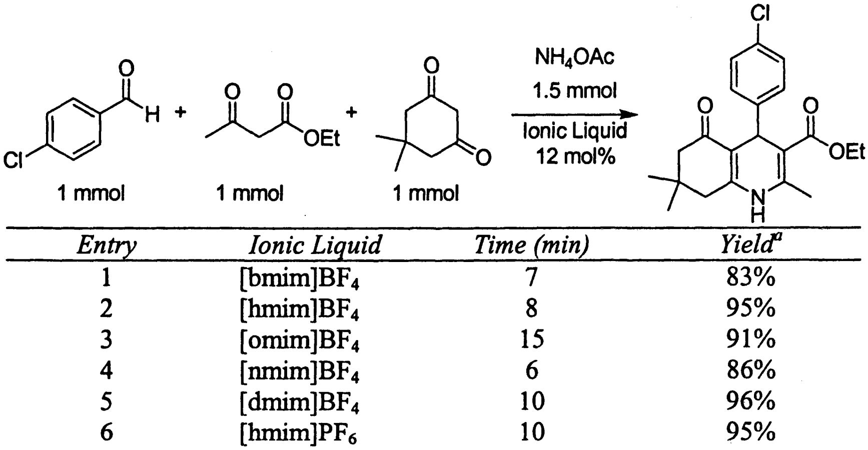


Scheme 1. Ionic liquid-catalyzed four-component synthesis of polyhydroquinoline derivatives in neat condition.

We screened through this reaction with various ionic liquids at 90°C. The results are shown in Table 121. We found that [hmim]BF_4 (Table 121, entry 2) gave us the best yield in the shortest reaction time.

Table 12. Ionic liquid-catalyzed four-component synthesis of polyhydroquinoline derivatives in neat condition.



Entry	*Ionic Liquid*	*Time (min)*	*Yield*[a]
1	[bmim]BF_4	7	83%
2	[hmim]BF_4	8	95%
3	[omim]BF_4	15	91%
4	[nmim]BF_4	6	86%
5	[dmim]BF_4	10	96%
6	[hmim]PF_6	10	95%
7	[hmim]Br	12	96%

[a] Isolated yield.

Considering the reaction time and yield, [hmim]BF_4 was selected as the optimum catalyst for this reaction (Table 121, entry 2). We then continued our study using various aldehydes with catalytic amounts of [hmim]BF_4. The results are summarized in Table . The reactions with both aliphatic and aromatic aldehydes went smoothly and gave the desired products in high yields (89% to 96%).

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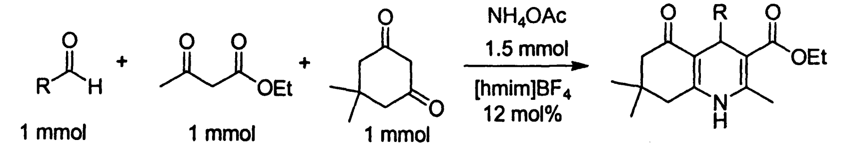
Table 13. [hmim]BF_4-catalyzed synthesis of polyhydroquinoline derivatives with various aldehydes.



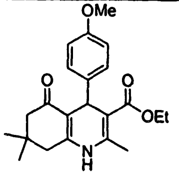
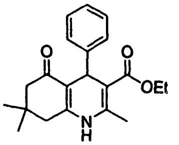
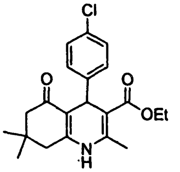
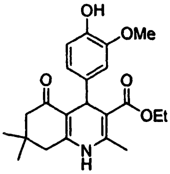
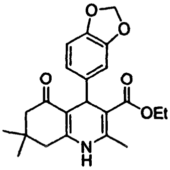
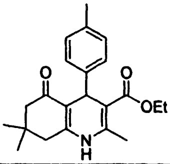
Entry	*Product*	*Time (min)*	*Yield*[a]	*Mp(°C)*	
				Obtained	*Reported(31f,32)*
1		9	96%	260–261	263–264
2		10	95%	227–229	2654–226
3		8	95%	246–247	245–246
4		10	94%	235–137	210–212
5		5	94%	251–253	197–199
6		12	93%	267–268	297–298

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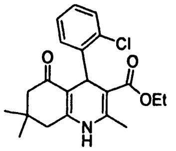
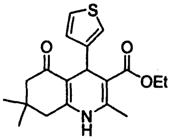
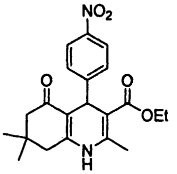
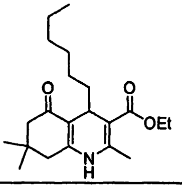
Table 13. *Continued.*

Entry	*Product*	*Time (min)*	*Yield*[a]	*Mp(°C)*	
				Obtained	*Reported(31f,32)*
7		26	92%	208–210	--
8		15	91%	248–250	--
9		14	91%	242–244	--
10		18	89%	153–154	--

[a] Isolated yield.

In short, we have developed an efficient [hmim]BF_4-catalyzed four-component condensation reaction of dimedone with various aldehydes, ammonium acetate and ethyl acetoacetate to form polyhydroquinoline in high yields.

Conclusion

In addition to our previous investigations on ionic liquids, our group has effectively developed useful methodologies for allylation reactions. We have also investigated the synthesis of bis(indolyl)methanes and polyhydroquinoline derivatives using ionic liquids. We strongly believe that the simplicities of all these methods have provided easy access and effective pathways to synthesize synthetically useful organic compounds. In conclusion, we envisage that the use of ionic liquids will continue to attract attention in years to come.

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Chapter 15

Ionic Liquids: Neoteric Solvents for Organic and Biocatalytic Transformations

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Abstract: The chapter deals with synthetic transformations in chlorolauminate ionic liquids highlighting the merits of these highly solvating Lewis acidic media. The preliminary investigations followed by later developments in the realm of biocatalytic transformations in neutral ionic liquids are also well within the scope of this chapter.

The 'ionic liquids', the term which is now very well-known to the chemists was once very remote in the chemical literature. This is because their existence and consequently their potential as a solvent was not recognized before. But, the ionic liquids are not very new as it seems, some of them have been known for many years. For instance $[EtNH_3][NO_3]$, which has a melting point of 12 °C, was first described in 1914! (*1*). However, one of the important development recorded in the chemical literature about these ionic liquids and their existence was in 1940. The two US scientists, Tom Weir and Frank Hurley working in the Rice Institute on liquid electrolytes accidentally prepared chloroaluminate ionic liquid which belongs to a class of ionic liquids now known as the first generation ionic liquids. However, the chemists of those times hardly noticed the potential of these astonishingly important liquids. In late 1980s, the scientists working in the US Air Force Academy were instrumental in initiating the preliminary research in the realm of ionic liquids. The eminent scientists such as King and Wilkes and associates can be regarded as the beginners of seminal work on ionic liquids which involved the synthesis of structurally diverse ionic liquids,

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their characterization, investigation of physical properties and so on (*2*). However, the ground breaking development from the point of view of an organic chemist was the investigation of Friedel-Crafts reaction in chloroaluminate ionic liquid (*3*). After this report, a renaissance of the rich chemistry of ionic liqiuids began. The pioneering work of Seddon and his associates introduced the ionic liquids to the modern day's chemists (*4*). Untill 2001, the chlorolauminate ionic liquids by far have been most widely explored class of ionic liquids. Later the spotlight shifted to a class of neutral, air and moisture stable ionic liquids very frequently referred to as second generation ionic liquids. Since then the cascade of reports on investigation of different reactions in ionic liquids began to appear in the chemical literature (*5,6*).

Chloroaluminate Ionic Liquids: the First Generation Ionic Liquids

The chloroaluminate ionic liquids or the first generation ionic liquids, are prepared by mixing the quaternary ammonium salts such as 1-butyl-3-methylimidazolium chloride with $AlCl_3$ (*7*). The apparent mole fraction of $AlCl_3$, *N* in these liquids dictates the behavior of the liquid as a Lewis acid catalyst. The mole fraction of $AlCl_3$, *N* between 0.33 to < 0.5 furnishes basic, 0.50 gives neutral and >0.50 to 0.67 or higher, yields Lewis acidic ionic liquid. It is the later variety of chloroaluminates that is useful for driving the Lewis acid catalyzed reactions. The liquidus range (the range of temperatures in which the compound exists in liquid state) depends on the structure of the cation and the mole fraction of $AlCl_3$. The interesting property of these liquids is that they provide a distinctly homogenous Lewis acidic medium in contrast to the conventional Lewis acid, $AlCl_3$ that is used for the reactions. After the execution of the Friedel-Crafts reactions by Wilkes *et al.* several electrophilic substitution reactions such as acylation of ferrocene, chlorination, nitration, etc were investigated (*1*).

Among the other reactions investigated, the Fries rearrangement, a typically Lewis acid catalyzed reaction was also executed in these ionic liquids. In order to realize the advantages of the chlorolauminate ionic liquids in the Fries rearrangement reaction, 1-butyl-3-methylimidazolium chloroaluminate, [bmim]Cl.xAlCl$_3$ (x = 1-2) was used as a solvent and Lewis acid catalyst for Fries rearrangement reaction of phenyl benzoates (Figure 1) (*8*). The [bmim]Cl.2AlCl$_3$ ionic liquid fetched good yields of the products at 120 °C within 2 hrs. The interesting feature observed was that the variation in the Lewis acidity of the ionic liquid and temperature influenced the overall yields as well as the *ortho* to *para* ratio (*o*/*p*) of the product formed in the reaction. The extent of conversion of phenyl benzoate was found to be the function of the Lewis acidity of ionic liquid. An increase in the Lewis acidity of the ionic liquid favored the *para* product. The kinetic investigations revealed that the rate of consumption of phenyl benzoate obeyed the first-order kinetics. Higher regioselectivities were observed in [bmim]Cl.2AlCl$_3$ at different temperatures.

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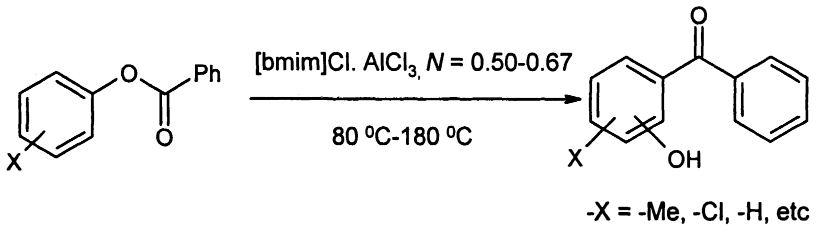

Figure 1. Fries rearrangement in chloroaluminate ionic liquids

The Friedel-Crafts sulfonylation reaction of benzene and substituted benzenes with 4-methyl benzenesulfonyl chloride in [bmim]Cl.xAlCl$_3$ was reported (Figure 2) (*9*). The substrates exhibited enhanced reactivity, furnishing almost quantitative yields of diaryl sulfones, under ambient conditions. Studies concerning the effect of Lewis acidity of the ionic liquid on the initial extent of conversion of this reaction, revealed a progressive increase in the initial rates of the reactions, due to consequent increase in the concentration of the catalytic species in the ionic liquid. The interesting insights in to the mechanistic details of the reaction in these liquids were investigated with the aid of ^{27}Al NMR spectroscopy. The studies reveal that the reaction takes place between the Lewis acidic species, $[Al_2Cl_7]^-$ and HCl, formed during the course of electrophilic substitution. Due to this, the catalytic species is converted to $[AlCl_4]^-$ and is no more available for catalysis. Some preliminary attempts to prevent this reaction in order to make these ionic liquids recyclable, did not succeed. However, the authors believe that if a suitable way is devised to prevent this reaction, the chlorolauminate ionic liquids could very well revolutionize the Friedel-Crafts chemistry.

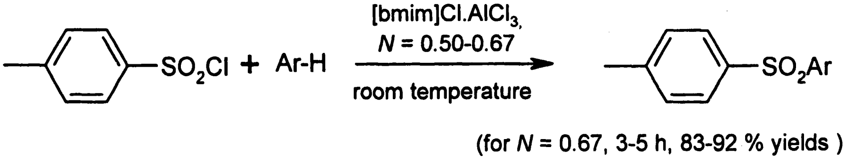

Figure 2. Friedel-Crafts sulfonylation in chloroaluminate ionic liquids

The Knoevenagel condensation, a useful reaction for the synthesis of electron deficient olefins, was found to work efficiently and expeditiously in [bmim]Cl.2AlCl$_3$, and [bpy]Cl.2AlCl$_3$ ionic liquids. The condensations of benzaldehyde and substituted benzaldehydes with diethyl malonate gave benzylidene malonates (Figure 3) (*10*). The optimized protocol fetched almost quantitative conversions with respect to decay of benzaldehydes. However, the

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benzylidene malonates subsequently underwent Michael additions with diethyl malonate. This side reaction was more pronounced in case of aldehydes with an electron releasing group at *para* position. Higher molar proportions of the ionic liquid favors the formation of the Knoevenagel over the Michael product. The declined *K/M* was observed as the Lewis acidity of the ionic liquid increased. An increase in the proportion of the ionic liquid increased the *K/M* ratio. The conversions in [bpy]Cl.2AlCl$_3$, ionic liquid were relatively less with relatively lower *K/M* ratios than what were observed in [bmim]Cl.2AlCl$_3$.

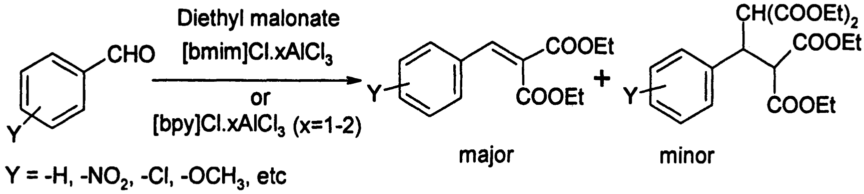

Figure 3. Carbonyl-methylene condensation in chloroaluminate ionic liquids

The coumarin synthesis was extended in these liquids via Pechmann condensation route (*11*). The protocol was found to be the most expeditious route (10 min), overcoming the disadvantage of demethylation in case of methoxy phenols, which is often observed in the protocol using AlCl$_3$ (Figure 4). Further, the authors also demonstrated the synthesis in neutral ionic liquids circumventing the limitations of the previous protocol.

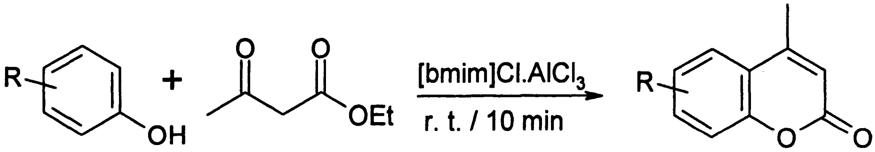

Figure 4. Pechmann condensation in chloroaluminate ionic liquids

A search for the suitable catalyst to induce direct synthesis of sulfoxides from arenes and thionylchloride, avoiding side reactions such as chlorination has been scarcely successful. An ionic liquid [bmim]Cl.2AlCl$_3$ mediated protocol proved to be a useful and advantageous addition to the reported methods (*12*). The experimental procedure is simple and time saving furnishing diaryl sulfoxides in near quantitative yields within 5 min (Figure 5).

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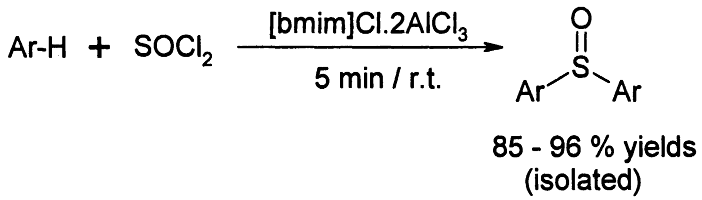

Figure 5. Sulfoxide synthesis in chloroaluminate ionic liquid

Few of the many interesting reports published pertaining to the usefulness of chlorolauminate ionic liquids for several organic transformations involve a practical and convenient protocol using [emim]Cl.$AlCl_3$, N = 0.67-0.75 for the synthesis of the novel 3-acylated indoles starting with the *N*-unprotected indoles (*13*). Deng *et al.* reported a novel cyclisation reaction of 1-dodecene to cyclodecane with high selectivity under moderate pressure in chloroaluminate ionic liquid (*14*). It was demonstrated that the solvent duo of EtOH and chloroaluminate ionic liquid provides a homogenous catalytic medium for the reaction, from which the products can be separated by merely raising the temperature of the reaction mixture, which is required for the separation of phases. The use of 1-butyl-pyridinium chloroaluminate ionic liquid for Fischer-Indole synthesis of ketones with aryl hydrazones has been demonstrated (*15*). The amount of ionic liquid required for the process is equimolar with respect to the ketone used for the reaction. In addition to this, the method does not require the catalyst in high concentrations as is often required in the protocols employing PPA and $ZnCl_2$. Wasserscheid *et al.* demonstrated the use of the buffered chloroaluminate ionic liquid as solvent for the catalyst, [(cod)Ni(hfacac)] known to produce the linear dimers from 1-butene (*16*). The dissolution of the catalyst resulted in the enhancement of the activity of the catalyst. The buffered chloroaluminates also takes care of the dimer selectivity and product linearity. An added advantage of the method is that being a biphasic process, easy catalyst recovery and recyclability is possible. Singer *et al.* used [emim]I.$AlCl_3$ as a solvent and catalyst for the acylative cleavage of cyclic and acyclic ethers in presence of benzoyl chloride as an acylating agent (*17*). Bifunctionalised α,ω-iodobenzoates have been isolated as the products from the reaction mixture from the cleavage of the cyclic ethers. The Lewis acidic 1-butyl-3-methylimidazolium chloroaluminate ionic liquid [bmim]Cl.$AlCl_3$, N = 0.67, has also been employed by us as a catalyst as well as the solvent for the quick and efficient syntheses of aryl keto acids by Friedel-Crafts acylation and aroylation of aromatic hydrocarbons using cyclic acid anhydrides (*18*).

Recently a new protocol was developed for the synthesis of *N*-substituted thioamides employing arenes and isothiocyanates in [bmim]Cl.2$AlCl_3$ as a homogenous Lewis acid catalyst and solvent (Figure 6) (*19*). Studies reveal that a progressive increase in yields was observed with increasing Lewis acidity and two equivalents of [bmim]Cl.2$AlCl_3$ was optimal

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amount for reaction. A distinct *para*-selectivity for the incoming thioamido group on activated arenes was observed under ambient conditions. The protocol eliminates the use of conventional obnoxious or volatile solvents such as halogenated hydrocarbons, nitromethane and carbon disulphide. Homogenous catalysis, reduced reaction times, and ambient conditions are some of distinctively notable advantages offered by the novel procedure.

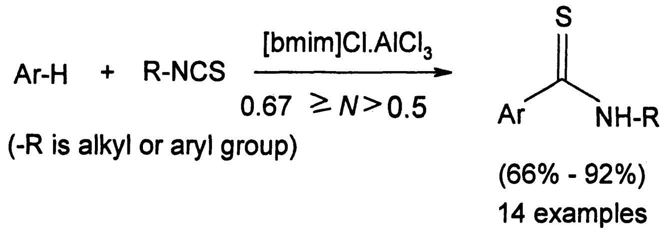

Figure 6. Friedel-Crafts addition of arenes to isothiocyanates in chloroaluminate ionic liquids

Further the ionic liquid, [bmim]Cl.$AlCl_3$, N = 0.67 mediated syntheses of aromatic sulfonamides via electrophilic substitution of arenes has been investigated (Figure 7) (*20*). The protocol serves as a distinctly expeditious and ambient route towards the syntheses of these pharmaceutically useful compounds, yielding quantitative conversions at room temperature within 5-30 min in most of the cases. The method has been used for the syntheses of a diverse range of sulfonamides by variation of arenes and sulfamoyl chlorides. With monosubstituted benzenes, the protocol offers an added advantage of exclusive selectivity towards the formation of *para*-substituted sulfonamides over the *ortho* products.

To list a few of many other applications where the chloroaluminate ionic liquids have been used include their application in alkylation of isobutene and butane (*21*), cleavage of methyl esters of flavones (*22*), DABCO-catalyzed

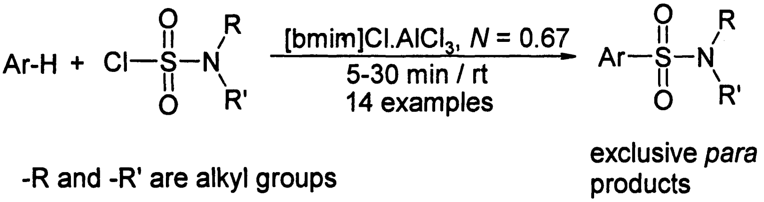

Figure 7. Friedel-Crafts sulfamoylation in chloroaluminate ionic liquid

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Baylis-Hillman reactions (*23*), endo-selective Diels-Alder reaction (*24*), the dimerization of 1,3-cyclopentadiene (*25*), Baeyer condensation (*26*), Prins cyclizations (*27*), cleavage of aromatic methyl ethers (*28*), oligomerisation of olefins (*29*), ring-opening polymerization of ethylene carbonate (*30*), Nickel(II) heterocyclic carbene complexes mediated olefin dimerization (*31*), selective hydrogenations (*32*), synthesis of transition metal cyclophane complex (*33*) and synthesis of organometallics (*34*).

Ionic Liquids: Promising Solvents for Biocatalytic Reactions

Almost two decades back when the potential of the neutral ionic liquids as the reaction media was not even conceptualized, Adams *et al.* in 1984 demonstrated the stability of alkaline phosphatase in aqueous solution of quarternary salt. The authors found that the enzymes were relatively stable in a mixture of tetraethylammonium nitrate and water in ratio 4:1 (*v/v*) (*35*). However, with an increasing consciousness regarding these ionic liquids, the enzymic scientists obviously became curious about the behavior of enzymes in these neoteric solvents. This led to a rapid development of biocatalytic research in these ionic liquids as indicated by some of the examples below.

Lye *et al.* came out with the first report on multiphase bioprocess operation employing the present days second generation room temperature ionic liquids as replacements for the conventional organic solvents (*36*). The ionic liquid, [bmim][PF_6]-water was successfully employed as a liquid-liquid biphase for the *Rhodococcus* R312 catalyzed biotransformations of 1,3-dicyanobenzene. The authors discovered that the greater specific activity of the biocatalyst in H_2O-[bmim][PF_6] system almost by an order of magnitude than in H_2O-toluene system. Shortly, thereafter a report appeared by the Erbeldinger *et al.* which was the first report demonstrating the use of isolated, cell free enzyme in ionic liquid. As a model reaction, *Z*-aspartame was synthesized in a thermolysin catalyzed reaction of carbobenzoxy-*L*-aspartate and *L*-phenyl alanine methylester hydrochloride in [bmim][PF_6] containing 5% (*v/v*) H_2O (*37*). Besides, the authors have also demonstrated that the enzyme (which otherwise requires immobilization) exhibits outstanding stability in this novel medium.

Sheldon *et al.* demonstrated that *Candida antarctica* lipase is able to catalyze a variety of transformations such as transesterifications, aminolysis and perhydrolysis in two different ionic liquids, [bmim][PF_6] and [bmim][BF_4] in absence of water (*38*). The reactions were executed with free (NOVO SP525) or immobilized enzyme (Novozyme 435). The reaction rates were comparable with or better than those observed in the conventional organic media. For example, the reaction of octanoic acid with ammonia in [bmim][BF_4] at 40 °C gave complete conversion to octanamide in 4 days compared to 17 days for the same conversion using ammonium carbamate in methyl isobutyl ketone. The epoxidation of cyclohexene by peroxy octanoic acid, generated in situ by

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Novozyme 435 catalyzed reaction of octanoic acid with 60% aq. H_2O_2 proceeded smoothly in [bmim][BF_4]. Kragl and coworkers investigated the kinetic resolution of 1-phenyl ethanol with nine different lipases in ten different ionic liquids (*39*). A variety of ionic liquids comprising of cations such as $[bmim]^+$, $[mmim]^+$, $[4mbpy]^+$ and anions such as PF_6^-, BF_4^-, TfO^-, MsO^-, BzO^- and Tf_2N^- were prepared and employed as the reaction media for transesterification of a *rac*-1-phenylethanol. Surprisingly, with the lipases from *Pseudomonas sp.* and *Alcaligenes sp.* the enantioselectivity for the formation of acetate was improved to a large extent as compared to the reaction in methyl *tert* butyl ether (MTBE).

Itoh *et al.* reported lipase-catalyzed enantioselective acylation of allylic alcohols in ionic liquids using vinyl acetate as an irreversible acyl donor (*40*). The authors observed that the rate of acylation was strongly dependant on the anionic part of the ionic liquid. While the *Candida antarctica* catalyzed acylation proceeded with high enantioselectivity in all the solvents tested, the reaction rates in [bmim][BF_4] were nearly equal to that observed in diisopropyl ether. Similarly, Kim and coworkers observed markedly enhanced enantioselectivities in the lipase *Pseudomonas cepacia* and *Candida antarctica* catalyzed transesterifications of various secondary alcohols in ionic liquids [emim][BF_4] and [bmim][PF_6] (*41*). Upon comparison of the enantioselectivity in ionic liquids and organic solvents, toluene and THF, it was found that relatively lipases were upto 25 times more enantioselective in ionic liquids. In the best experiments, the enantiomeric ratio greater than 1000 was observed in *Pseudomonas cepacia* catalyzed reactions in [bmim][PF_6]. The lipase activity in ionic liquids was found to be as good as or slightly lower than in organic solvents.

Kim *et al.* further extended the investigation of enantioselectivity of lipase catalyzed reactions in ionic liquids. In a different strategy, a new type of immobilization protocol was devised wherein the ionic compound, 1-(3'-phenylpropyl)-3-methylimidazolium hexafluorophosphate, which is liquid above 53 °C was mixed with the enzyme in its liquid state and then solidified. The preparation so obtained was referred to as Ionic Liquid-Coated Enzyme (ILCE) and was used in organic solvents for enantioselective acylation of alcohols. This preparation of *Pseudomonas* lipase exhibited markedly enhanced enantioselectivity in almost all the cases when compared with the native form of the enzyme (*42*).

The ionic liquid, 1-ethylpyridinium trifluroacetate, [epy][CF_3COO] was employed by Malhotra *et al.* for the protease catalyzed resolution of *N*-acetyl amino acid esters (*43*). The products with *ee* between 86-97 % were realized in an optimized protocol. Kazlauskas *et al.* reported an improved method of preparation of ionic liquids, which were found to be more suitable for the lipase catalyzed biotransformations (*44*). The lipase-catalyzed reactions that previously did not occur in untreated ionic liquid, now occur at the rates comparable to those in the non-polar organic solvents such as toluene. The acetylation of 1-

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phenylethanol catalyzed by lipase from *Pseudomonas cepacia* was as fast and as enantioselective in ionic liquids as in toluene. The acetylation of glucose mediated by CAL was attempted in ionic liquids since it was found to be almost 100 times more soluble in ionic liquids than in organic solvents.

The lipase-catalyzed transesterifications of 2-hydroxymethyl-1,4-benzodioxane in two different ionic liquids, 1-butyl-3-methylimidazolium hexafluorophosphate, [bmim][PF_6] and 1-butyl-3-methylimidazolium tetrafluoroborate, [bmim][BF_4] and different organic solvents were investigated to decipher the influence of these neoteric solvents on lipase activity. (Figure 8) (*45*). The hydrophobic and hydrophilic properties of ionic liquids and organic solvents influenced the lipase activity as gauged in terms of the rate of transesterification. The influence of the ionic liquid as an additive in an organic solvent on this reaction has been demonstrated. The supported lipase and the [bmim][PF_6] ionic liquid was found to be the best combination for the said reaction. The enzymes in ionic liquids in combination were recycled for several runs without substantial diminution in the lipase activity.

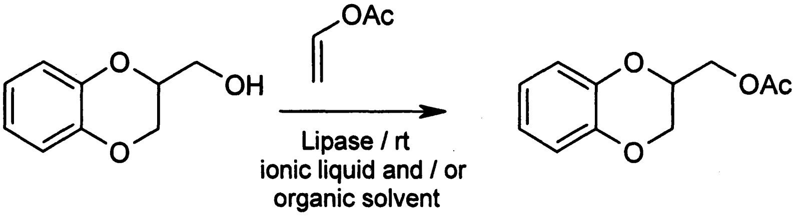

Figure 8. Lipase-catalyzed transesterification of 2-hydroxymethyl-1,4-benzodioxane

The supported lipase *Pseudomonas cepacia*, catalyzed aliphatic polyester synthesis in 1-butyl-3-methylimidazolium hexafluorophosphate ionic liquid as a novel reaction medium was investigated (*46*). Lipase PS-C demonstrated remarkable compatibility with the novel reaction medium by exhibiting excellent catalysis in polycondensation of diethyl octane-1,8-dicarboxylate with 1,4-butanediol at room temperature (Figure 9). Lipase exhibited high initial rate of transesterification as indicated from the rapid initial consumption of the monomer, diethyl octane-1,8-dicarboxylate. The average molecular weight of the polymer formed was limited to around 2270 at room temperature. A relatively high molecular weight polymer was obtained in relatively shorter reaction times at 60 °C. Based on the results it was perceived that to certain extent it is possible to excercise control over the molecular weight of the polymer obtained, by employing the ionic liquid possessing the properties streamlined for the purpose.

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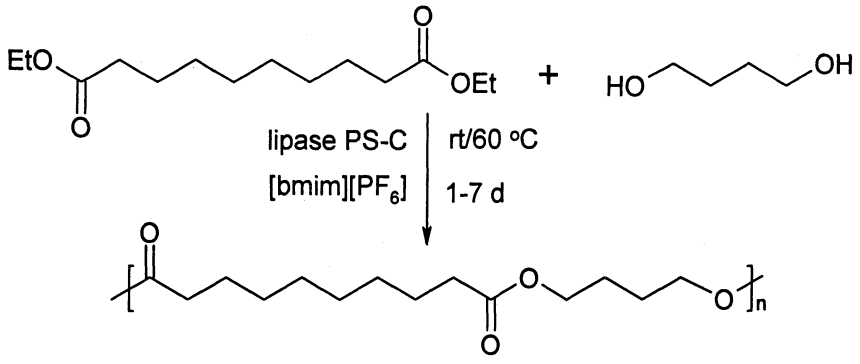

Figure 9. Lipase-catalyzed polyester synthesis in ionic liquid

Russell *et al.* carried out the solvatochromic analysis of ionic liquids and the partition coefficient data obtained suggests that the ionic liquids are highly polar and hydrophilic in nature in comparison to the organic solvents such as hexane, acetonitrile and THF (*47*). In the transesterifications studied, the activity of free lipase was found to be greater in [bmim][PF_6] than in hexane. The conventional methods of enzyme stabilization proved to be ineffective in the hydrophilic ionic liquids. Reversible inactivation of lipase was observed in AcO^- and MsO^- based ionic liquids, where as NO_3^- based ionic liquids were found to inactivate lipase irreversibly. Bartsch *et al.* further investigated the ionic liquid-*Sc*CO_2 combination for the execution of lipase catalyzed transesterification of vinyl butyrate and 1-butanol to butyl butyrate (*48*). Here the potential advantage of *Sc*CO_2 of differential solubilities at different pressures in ionic liquid was exploited for execution and subsequently product separation. The ionic liquids employed were [emim][NTf_2] and [bmim][NTf_2] and immobilized CAL B lipase on glass wool. At lowest pressures of ScCO_2, least enzyme deactivation of about 15% was observed. Greater than 99.9% *ee* was observed in the enantioselective acylation of 1-phenyl ethanol with vinyl propionate as acyl donor. In different approaches attempted (which included packed bed reactor and continuous flow) good yields of the products were realized indicating the compatibility of the enzyme to the biphasic ionic liquid-*Sc*CO_2 system which offered some practical advantages such as easy product separation, recyclability and potential large scale commercial applications. Iborra *et al.* demonstrated that the *Candida antarctica* lipase B dissolved in ionic liquids [emim][NTf_2] and [bmim][NTf_2] combined with ScCO_2 displayed good catalytic activity, enantioselectivity and operational stability for both butyl butyrate synthesis and kinetic resolution of 1-phenylethanol by transesterification under anhydrous conditions (*49*). The authors suggested that the ionic liquids provide the enzyme with an adequate microenvironment allowing high activity and continuous reuse as observed in the continuous packed bed reactors. The authors also found that the activity decay was enhanced by an increase in the temperature.

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Iborra *et al.* carried out CAL mediated butyl butyrate synthesis in $[NTf_2]^-$ based ionic liquids with 2% by volume of H_2O at 50 °C (*50*). Enhanced activity was observed compared to the organic solvents. The authors observed a distinct over-stabilization of enzyme in the continuous operations, which they believe is because of the ionic environment provided by the ionic liquids. Reetz *et al.* reported CAL catalyzed transesterification of 1-octanol and kinetic resolution of phenylethanol in ionic liquids using *Sc*CO_2 as a mobile phase in batch wise or continuous flow operations (*51*).

Gubicza *et al.* successfully applied ionic liquids as solvents for enantioselective esterification of 2-choloropropanoic acid with 1-butanol using *Candida rugosa* lipase (*52*). The role of H_2O produced during the reaction and the control of H_2O activity with per-vapouration was studied. Under the optimal conditions of H_2O activity the lipase exhibited high thermal stability in ionic liquid and it could be reused for at least 5 cycles with only a small loss in the activity. The enzymes displayed much reduced activity in hexane than in ionic liquid in the repeated runs. Howarth *et al.* reported bioreductions with immobilized Baker's yeast of a series of ketones in [bmim][PF_6]/water taken in 10/1 ratio (*53*). In terms of enantioselectivities offered by protocol, the method is comparable to those known in literature.

The racemic secondary alcohols were resolved via lipase ***Pseudomonas cepacia*** supported on celite (PS-C) catalyzed enantioselective acylation using succinic anhydride as acyl donor in ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF_6] (Figure 10) (*54*). Further, triethylamine was found to be an efficient additive in ionic liquid to enhance the rate of the said enantioselective acylation reaction.

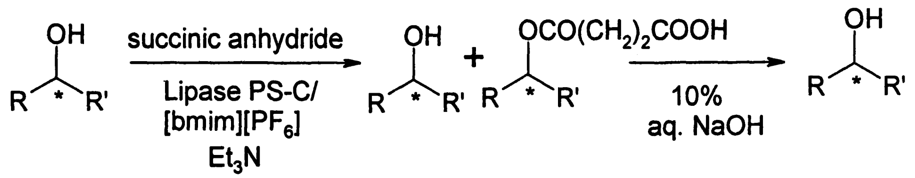

Figure 10. Lipase-mediated enantioselective acylation of secondary alcohols in ionic liquid

Lipase mediated regioselective biotransformations such as hydrolysis and alcoholysis of 3,4,6-tri-*O*-acetyl-D-glucal, have been studied in organic solvent, tetrahydrofuran and two different ionic liquids, [bmim][PF_6] and [bmim][BF_4] (Figure 11) (*55*). The ionic liquids as the reaction media substantially influenced the rates and regioselectivity of enzyme catalysis. A marked regioselectivity towards the formation of 4,6-di-*O*-acetyl-D-glucal, was observed in [bmim][PF_6] with 84% product formation after 6 h with 98% selectivity in hydrolysis and

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48% after 8 h with 98% selectivity in alcoholysis. Contrary to this, the other ionic liquid [bmim][BF_4] did not prove to be the medium of choice at all for any of these transformations.

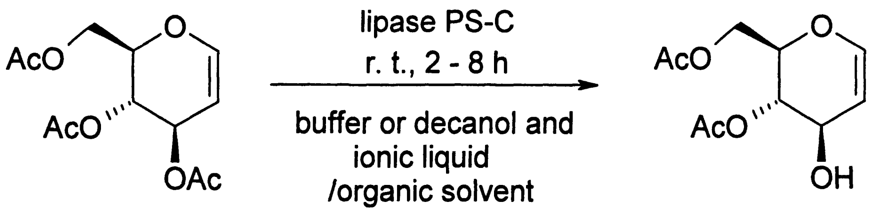

Figure 11. Lipase-catalyzed regioselective hydrolysis and alcoholysis of 3,4,6-tri-O-acetyl-D-glucal in ionic liquid

The *Candida rugosa* lipase-catalyzed enantioselective hydrolysis of butyl 2-(4-chlorophenoxy)propionate has been carried out in aqueous buffer with ionic liquid as co-solvent (Figure 12) (*56*). The markedly enhanced enantioselectivity towards the *R*-enantiomer of substrate was observed under the optimum additive conditions (1:1 composition of ionic liquid and buffer). The hydrophobic ionic liquids offered almost quantitative conversions with ee ≥ 99%.

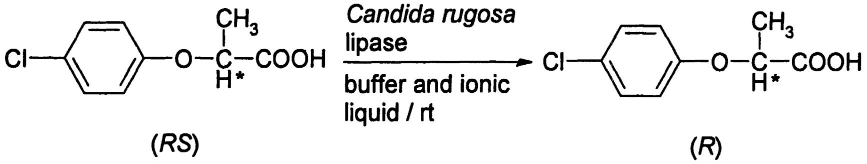

Figure 12. Lipase-catalyzed enantioselective hydrolysis of butyl2-(4-chlorophenoxy)propionatein ionic liquid

The arena of the organic biocatalytic transformations in ionic liquids has been very well reviewed earlier by the eminent chemists active in this field encompassing very fine pieces of work (*57,58*). Apart from the examples mentioned above, the other examples of enzymatic reactions in ionic liquids include the dynamic kinetic resolution of secondary alcohols by enzyme-metal combinations in ionic liquid (*59*), enantioselective acylation of amines (*60*), continuous flow enzymatic kinetic resolution and enantiomer separation using ionic liquid-supercritical carbon dioxide media (*61*), enantioselective transport of (*S*)-ibuprofen through a supported liquid membrane based on ionic liquids (*62*), selective acylation of glycosides in ionic liquids (*63*), 1-butyl-2,3-

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dimethylimidazolium tetrafluoroborate facilitated transesterification using vinyl acetate as acyl donor (*64*), esterification integrated with pervaporation for removal of water (*65*), resolution of homophenylalanine ester (*66*), ester synthesis (*67*), use of oxidative enzymes (*68*), β-galactosidase catalyzed synthesis of *N*-acetyllactosamine (*69*), resolution of racemic P-chiral hydroxymethanephosphinates and hydroxymethylphosphine oxides (*70*), stereoconvergent hydrolysis of *trans*-β-methylstyrene oxide, (*71*) etc.

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Chapter 16

Toward Green Processes for Fine Chemicals Synthesis: Biocatalysis in Ionic Liquid–Supercritical Carbon Dioxide Biphasic Systems

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Enzymatic transformations in ionic liquids (ILs)/supercritical carbon dioxide ($scCO_2$) biphasic systems, whereby enzyme molecules are "immobilized" in the IL phase and substrates/products are transported by the $scCO_2$ phase, are described as a way for carrying out clean synthetic chemical processes to produce pure products, being. Task-specific ionic liquids (TSILs), based on quaternary ammonium cations, with functional side chains (trimethylydroxylpropyl-, trimethylbutyronitryl-, trimethylhexylonitryl-, trimethylbutyl- and trimethylhexyl-), associated with the same anion (bis(trifluoromethane)sulfonylamide), were assayed for *Candida antarctica* lipase B (CALB)-catalyzed ester synthesis in IL/$scCO_2$ biphasic systems. The suitability of these ILs was established from both the activity and stability of the enzyme, including the maintenance of the secondary structure of the protein using circular dichroism spectroscopy. The mass-transfer phenomena between IL/$scCO_2$ phases were found to be key parameters for the efficient design of synthetic processes in these systems.

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Introduction

One of the challenges facing modern chemistry is the development new products, processes and services that provide the social, economic and environmental benefits both now and in the future *(1)*. This requires new approaches which properly set out to minimize or eliminate the release of harmful chemicals into the environment, to maximize the recyclability/reuse of reaction and extraction media, and to improve the efficiency of catalysts (*e.g.* their activity, selectivity and stability). For example, volatile organic solvents (VOSs) represented 66 % of all industrial emissions at 1997 in the USA *(2)*, while alternatives to traditional solvents that reflect the aims of green chemistry include ionic liquids (ILs) and supercritical fluids.

ILs are simply liquids composed entirely of ions at or close to room temperature. Their interest as green solvents resides in their high thermal stability and very low vapor pressure, which mitigate the problem of VOS emission in the atmosphere. Moreover, the physical properties of ILs (density, viscosity, melting point, polarity, etc.) can be finely tuned by the appropriate selection of anion, cation and/or attached substituents. Furthermore, ILs exhibit an excellent ability to dissolve polar and non-polar organic, inorganic and polymeric compounds, which explain the increasing attention paid to them as media for performing all types of organic reactions *(3, 4)*. In the same context, task-specific ionic liquids (TSILs), *i.e.* those with a targeted functionality designed into the cation or anion, have received much interest, because they can be designed to confer specific chemical or physical properties (*e.g.* extraction properties) *(5)*, which, associated with their recoverability and recyclability, are key features for developing green chemical processes *(6)*. One important problem with organic synthesis in ILs is the difficulty to recover reaction products. Extraction with IL-immiscible solvents, which are able to form biphasic systems, is a classical way of separating the products from the ILs phase. However, the loss of small amounts of the IL and/or catalyst represents an important limitation. In the same way, partitioning of the solute between the phases limits the extent to which solutes can be extracted and, obviously, the use of VOSs is a clear breakdown-point for the integral green design of the process.

Supercritical fluids are materials which operate at pressures and temperatures higher than their critical points: their densities are comparable to those of liquids, while their diffusivities and viscosities are similar to those of gases. Furthermore their solvent properties can be finely tuned by changes in either pressure and/or temperature, which make them ideal solvents for extractive processes. Carbon dioxide is the most popular supercritical fluid because of its relatively low critical parameters, low toxicity, and non-flammability, and is considered as a green solvent *(7)*. Supercritical carbon dioxide ($scCO_2$) has clearly been demonstrated to be a green alternative to VOSs due to its exceptional ability to extract a wide variety of hydrophophic compounds from certain ILs, since it is highly soluble in the IL phase, while the same IL is not measurably soluble in the $scCO_2$ phase *(8)*. Therefore, solutes dissolved in $scCO_2$ can directly be recovered by simple

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depressurization, after which CO_2 can be pressurized for reuse as solvent. In this context, there is a growing interest in developing systems for biphasic or phase separable catalysis, whereby a homogeneous catalyst is immobilized in the IL phase and reagents and/or products reside largely in the $scCO_2$ phase, as it is shown in Figure 1 *(9-11)*.

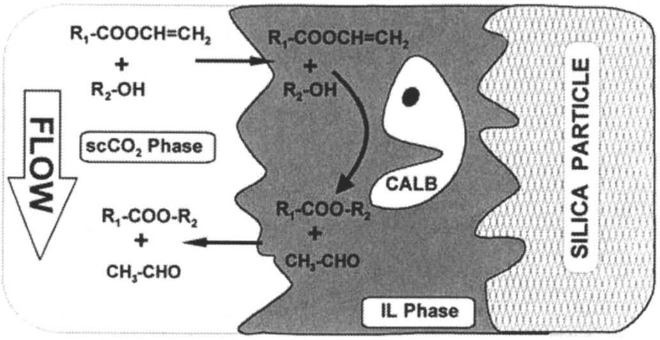

Figure 1. Scheme of continuous enzyme-catalyzed transesterification in IL-$scCO_2$ biphasic system.

Research into ways applying enzymes as catalysts in organic synthetic reactions under anhydrous conditions (*e.g.* organic solvents) has greatly increased during the past 15 years, especially in the case of asymmetric synthetic transformations due to the growing demand for enantiopure pharmaceuticals *(12)*. However, enzymes are catalytic proteins of living systems, designed to function in aqueous solutions within a narrow range of environmental conditions (pH, temperature, pressure, etc), and the use of organic solvents in biocatalytic reactions is seriously limited by their denaturing effect on proteins *(13)*. The feasibility of employing ILs as solvents in enzymatic catalysis has been extensively demonstrated by several research groups, who have obtained excellent results for many different chemical transformations, including ester synthesis *(14)*, kinetic resolutions *(15-17)* and carbohydrate ester synthesis *(18, 19)*. Certain ILs have shown themselves to be by far the best non-aqueous media for enzyme-catalyzed reactions because of the high level of activity they permits and the over-stabilization effect they have on the biocatalysts (up to 2,300-fold half-life time with respect to classical organic solvents) *(20-22)*. In the case of $scCO_2$, enzymes exhibit important deactivation phenomena as a result of direct contact with this neoteric solvent, which can be attributed to the chemical modification of proteins, local pH changes and/or conformational changes produced during the pressurization/ depressurization steps (*23, 24*). Enzymatic reaction media based on a combination of both types of neoteric solvent, *i.e.* ionic liquids and supercritical fluids, seem to be a promising way of developing integral green chemical processes in the near future *(11)*. Our previous work pointed to the efficiency of ILs in protecting the enzymes used for synthetic reactions in $scCO_2$, demonstrating that enzymes are not "soft" catalyst for continuous operation in organic synthesis

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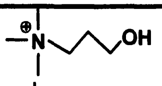
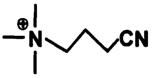
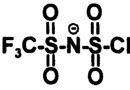
and can be used in clean processes, even under very extreme conditions, such as 10 MPa and 150°C *(9, 25, 26)*.

The aim of this chapter is to describe our efforts towards the design of green enzymatic processes in IL/$scCO_2$ biphasic systems, using an experimental strategy based on the study of three critical points: *(i)* the selection of suitable ILs, *(ii)* the catalytic behavior of the enzyme in ILs, and *(iii)* the role of mass-transfer phenomena between both IL/$scCO_2$ immiscible phases. As regards the first point, the miscibility of ILs with water needs to be considered in order to avoid the enzyme deactivation by "water stripping" phenomenon that occurs in polar organic solvents *(12, 13)*. No detectable enzyme activity was observed in several pure water-miscible ILs *(27)*, probably due to the strong hydrogen bond basicity of anions. In this context, five water-immiscible ILs with different hydrophobic characteristic were assayed. These ILs were based on quaternary ammonium cations bearing different functionalized side chains, (3-hydroxypropyl)-trimethyl [C_3OHtma], (3-cyanopropyl)-trimethyl [C_3CNtma], butyl-trimethyl [C_4tma], (5-cyanopentyl)-trimethyl [C_5CNtma], and hexyl-trimethyl [C_6tma], associated with the same anion (bis(trifluoromethane)sulfonyl amide [NTf_2] (see Table 1).

Table 1. Structures of assayed ILs and the Hansen's solubility parameter (δ) of the main chain cation.

Anion	*Cation*	*δ (MPa)$^{1/2}$*
	 C_3OHtma	23.0
	 C_3CNtma	21.5
 NTf_2	C_5CNtma	20.7
	C_4tma	15.6
	C_6tma	15.5

With respect to the second point, *Candida antarctica* lipase B (CALB) was chosen as biocatalysts because of the high number of chemical transformations previously described for this enzyme *(12)*, we studied its activity, enantioselectivity and stability for the kinetic resolution of *rac*-1-phenylethanol in the above ILs (see Figure 2). To support the enzyme stability results, a comparative analysis of changes in the secondary structure of the protein for different media was carried out by using circular dichroism (CD) spectroscopy.

Finally, the efficiency of CALB-catalyzed continuous green chemical processes in ILs/$scCO_2$ was also analyzed as a function of the assayed ILs to

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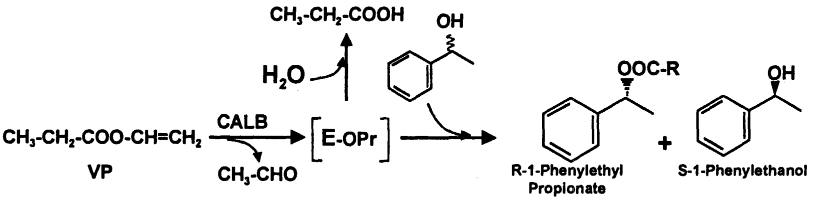

Figure 2. Enzymatic kinetic resolution of rac-1-phenylethanol.

ascertain the role of mass-transfer phenomena into the biphasic system, by using the synthesis of several short-chain alkyl esters as reaction models.

Materials and Methods

Materials

Soluble CALB (Novozym 525, EC 3.1.1.3, from Novo Nordik S.A.) was washed by ultrafiltration to eliminate all the low molecular weight additives, obtaining an enzyme solution of 14.9 mg/mL, as determined by Lowry's method. Silica gel (63-200 µm particle size, 6 nm pore diameter) was obtained from Sigma Chem. Co. Substrates, solvents and other chemicals were purchased from Sigma-Aldrich-Fluka Chemical Co, and were of the highest purity available.

Synthesis of ionic liquids

The assayed task-specific ionic liquids ((3-hydroxypropyl)-trimethyl ammonium (bis(trifluoromethane) sulfonyl amide or bistriflymide) [C_3OHtma] [NTf_2]; (3-cyanopropyl)-trimethylammonium bistriflymide [C_3CNtma] [NTf_2]; butyl-trimethylammonium bistriflymide [C_4tma][NTf_2], (5-cyanopentyl)-trimethylammonium bistriflymide [C_5CNtma] [NTf_2], and hexyl-trimethylammonium bistriflymide [C_6tma][NTf_2]) were synthesized as previously described in detail *(26)*. In all cases, starting reagents of the highest purity available were used to synthesize the ILs, operating with special care to reach final IL purities of higher than 99.8%, as determined by NMR (Bruker AC 300 P; ^{1}H: 300.13 MHz; ^{13}C: 75 MHz) and high resolution mass spectrometry (Micromass ZABSpec TOF). The residual water content of the synthesized ILs was lower than 200 ppm, as determined by the Karl-Fisher titration. The chloride content results undetectable by both mass-spectrometry and the $AgNO_3$ test.

Kinetic resolution of *rac*-1-phenylethanol

Twenty-two microliters (198 µmol) of vinyl propionate and 12 µL (99 µmol) *rac*-1-phenylethanol were added to screw-capped vials (1-mL total capacity) containing 162 µL of IL ([C_3OHtma][NTf_2], [C_3CNtma][NTf_2], [C_4tma][NTf_2],

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[C_5CNtma][NTf_2] or [C_6tma] [NTf_2]), or hexane. The reaction was started by adding 4 μL (14.9 mg CALB/mL water) and run at 50 °C in an oil bath, shaking for 1 hour. At regular time intervals, 15 μL aliquots were taken and suspended in 285 μL hexane. The biphasic mixture was rigorously shaken for 3 min to extract all the substrates and product into the hexane phase. For the hexane reaction medium, aliquots were dissolved in acetone:HCl (99:1 v/v) to stop the reaction. Samples were analyzed by GC. One unit of synthetic activity was defined as the amount of enzyme that produces 1 μmol of (*R*)-1-phenylethyl propionate per min. All the experiments were carried out in duplicate.

Stability of CALB in ILs by recycling operation

The substrates mixture (22 μL vinyl propionate and 12 μL *rac*-1-phenylethanol) was dissolved in 162 μL IL ([C_3OHtma][NTf_2], [C_3CNtma][NTf_2], [C_4tma][NTf_2], [C_5CNtma][NTf_2] or [C_6tma] [NTf_2]) in different screw-capped vials (1-mL capacity). The reaction was started by addition of 4 μL of a CALB solution (14.9 mg/mL water), and maintained at 50 °C with shaking for 1 h. All substrates and products were recovered by liquid-liquid extraction with hexane (1 mL). Finally, the hexane phase was collected for GC analysis and the IL phase was washed twice more with hexane (1 mL) to ensure that all the reaction products had been eliminated. Then another reaction was started by adding fresh substrate solution (22 μL vinyl propionate and 12 μL *rac*-1-phenylethanol) to the ionic liquid phase. This process was repeated, and the hexane phase was carefully collected to avoid loss in the enzyme-ILs phase. In the case of hexane, a mixture of 162 μl hexane and 4 μl CALB solution (14.9 mg/mL water) was incubated in the absence of substrates in the same conditions. Then, at selected times, the substrate solution (22 μL vinyl propionate and 12 μL *rac*-1-phenylethanol) was added, and the reaction was followed as described above.

Circular dichroism spectroscopy

Far-UV (190-240 nm) CD spectra (PiStar-180 spectrometer equipped with a Peltier system for temperature control, Applied Photophysics, UK) were obtained for 0.3 mg/mL CALB solutions in water at 50°C using 0.1 cm cells. CD calibration was performed using (1S)-(+)-10-camphorsulfonic acid (Aldrich), which exhibits a molar extinction coefficient of 34.5 *M*/cm at 285 nm, and molar ellipticity of 2.36 *M*/cm at 295 nm. Before the measurements, samples were preequilibrated at the desired temperature for 15 min, and the scan speed was fixed for adaptative sampling (error ± 0.01) with a response time of 1 s, and 1 nm bandwidth. Six spectra were acquired and averaged for each sample. For each solvent, it was necessary to subtract a blank medium without enzyme to discard its influence on the enzyme CD spectrum. Mean residue ellipticity ([θ]) was expressed in (deg cm^2/dmol residue), using 33,000 Da as molecular weights and, 317 residues for CALB, as obtained from Protein Data Bank

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(http://www.rcsb.org/pdb/). The percentages of secondary structures were calculated by using on line circular dichroism analysis, DICHROWEB (http://www.cryst.bbk.ac.uk/cdweb/html/), which provides several curve analyzing algorithms (*e.g.* CONTINLL; SELCON3, CDSSTR etc.) (*28*). The CDSSTR method was selected to determine the protein secondary structure of CALB, according to the best agreement between experimental and databank spectra of the native conformation.

Enzymatic reactions in ILs-scCO_2

One hundred microliters of CALB solution (14.9 mg/mL in water), were adsorbed in 300 mg of silica gel, and then 100 µL of ILs ([C_3CNtma][NTf_2] or [C_4tma] [NTf_2]) were added, covering all the wet silica particles. The final mixture was placed in the cartridge of an ISCO 220SX high pressure extraction apparatus of 10 mL total capacity. Alkyl ester synthesis was carried out by continuous pumping of an equimolar solution of pure substrates (5.47 M vinyl acetate (VA) and 1-butanol (BuOH), or 4.98 M vinyl propionate (VP) and BuOH, or 4.54 M vinyl butyrate (VP) and BuOH, or 4.19 M VP and 1-hexanol (HexOH), or 3.92 M VB and HexOH, or 3.68 M VP and 1-octanol (OcOH), respectively) at 45 µmol/min mass flow for each substrate (flow rates from 0.007 to 0.012 mL/min), and mixed with the scCO_2 flow of the system at 50 °C and 10 MPa (Figure 3). The reactor was continuously operated for 4 h. Substrates and products were fully soluble in scCO_2, and the reaction mixtures were recovered by continuous depressurizing through a calibrated heated restrictor (1 mL/min, 70 °C) in 30 minute steps. Samples were analyzed by GC. In all cases, substrate and product mass-balances from the outlet were consistent with the substrate mass-flow inlet.

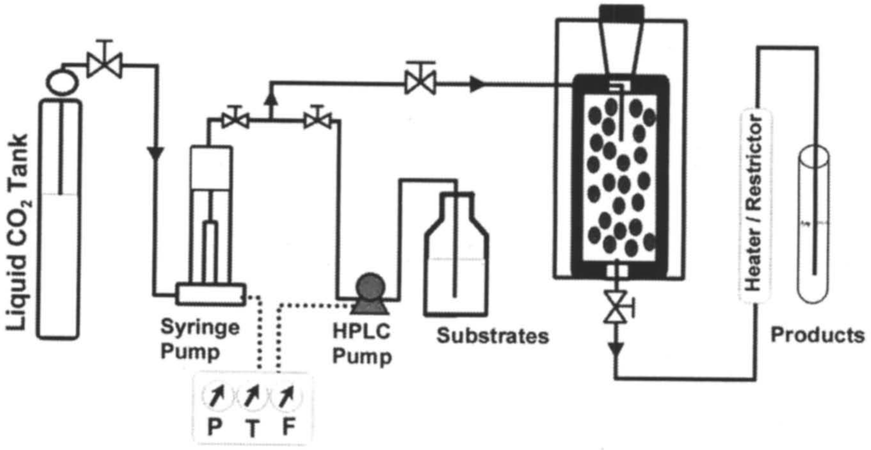

Figure 3. Experimental set-up of the continuous enzyme reactor with ILs-scCO_2.

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GC analysis

Analyses were performed with a Shimadzu GC-17A equipped with FID detector. In the kinetic resolution of *rac*-1-phenylethanol, samples were analyzed by a Beta DEX-120 column (30 m x 0.25 mm x 0.25 μm, Supelco) as described previously (*22*). For alkyl ester synthesis reactions, samples were analyzed by a semicapillary Nukol column (15 m x 0.53 mm x 0.5 μm, Supelco), using ethyl hexanoate (EH) as internal standard. The chromatographic conditions were as follows: carrier gas (He) at 9 kPa (40 mL/min total flow); temperature program: 40 °C, 4 min, 3 °C/min, 75 °C, 10 °C/min, 150 °C, split ratio, 98:1; detector, 220 °C. The retention time of the peaks was as follows: VA, 2.5 min; VP, 3.2 min; VB; 4.7 min; BA, 6.0 min; BP, 7.7 min; BuOH, 8.7; BB, 10.6 min; EH, 11.1 min; HP, 14.3 min; HexOH, 15.0 min; HB, 16.6 min; OP, 19.9 min; OcOH, 20.7 min , acetic acid, 21.0 min; propionic acid, 21.9 min; butyric acid, 23.1 min.

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Results and Discussion

CALB-catalyzed kinetic resolution of *rac*-1-phenylethanol in TSILs

The resolution of rac-1-phenylethanol catalyzed by a serine hydrolase (e.g. CALB) is a kinetically controlled process highly dependent on the nucleophile acceptors present in the reaction media. As can be seen in Figure 2, this process involves the competitive distribution of the rapidly formed acyl-enzyme intermediate between each of the nucleophiles present into the media: water and 1-phenylethanol. Water is the most powerful nucleophile, and is able to deacylate the intermediate to yield propionic acid as hydrolytic product. Thus, the ability of CALB-catalysis can be mainly expressed by two parameters, the synthetic rate and the ratio between this and the acyl donor consumption rate (selectivity). Additionally, in the case of a chiral acyl acceptor (e.g. *rac*-1-phenylethanol), the enantioselectivity of the enzyme towards one of the R- or S isomers is another important parameter, which can be measured by the R/S synthetic product rates ratio. Figure 4 shows the synthetic activity and selectivity exhibited by the enzyme in hexane and the different TSILs at 50 °C and 2 % v/v water content. As can be seen, all ILs were suitable reaction media for the proposed synthetic reaction. Considering the structure of the cation present in each TSIL, synthetic activity and selectivity parameters were gradually reduced by the increase in hydrophobicity of the functional side chain, except in the case of the most hydrophilic IL ([C_3OHtma] [NTf_2]), where the worst synthetic activity was reached. Since the selectivity parameter is a measure of the undesirable hydrolytic reaction, these results show the high efficiency of assayed TSILs compared with a classical organic solvent, like hexane (*17, 26*).

The differences in selectivity between TSILs could be attributed to their specific abilities to reduce water activity (Aw) in the enzyme microenvironment.

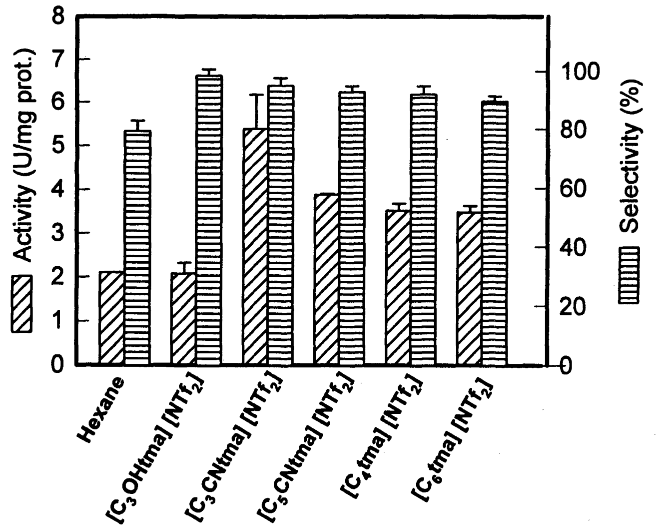

Figure 4. Synthetic activity and selectivity exhibited by CALB-catalyzed kinetic resolution of rac-1-phenyl ethanol in different TSILs at 2 % v/v water content and 50 °C.

Hence, an increase in the hydrophobicity of the IL results in an increase in free water molecules, which can act as nucleophile acceptors in the transesterification reaction, and so produce a loss in selectivity. Dupont (*29*) has reviewed the structural organization of ILs, describing how these neoteric solvents are able to form an extended network of ions connected by hydrogen bonds. Wet ILs are not regarded as solvents with homogeneous structures, but as nanostructures with polar and non-polar regions (*4*). In this context, an aqueous solution of free-enzyme molecules added to the IL phase could be regarded forming hydrophilic gaps in the network, providing an adequate microenvironment for the catalytic action (*21, 26*). So the increased concentration of free-water molecules in the hydrophilic gaps involves a reduction in selectivity. The equilibration of ILs with saturated salt solutions (*30*) has been assayed to control Aw in synthetic reactions catalyzed by lipases, but have resulted in changes in catalytic efficiency. In continuous processes, the excess of free water molecules can be consumed by the hydrolytic reaction during the earliest steps until an appropriate hydration level is reached in the enzyme (*25*), thus avoiding undesirable enzyme deactivation by excessive dehydration. The low activity level obtained for [C_3OHtma][NTf_2] could be attributed to disruption of the hydration shell around the protein by the strong hydrogen-bond interaction of the functional side chain of the cation with essential water molecules. In the same way, low or no activity has been described when enzymatic reactions are performed in water-miscible ILs at low water content (*27*).

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Stability of CALB in TSILs

Enzyme stability in these neoteric solvents was studied by an incubating aqueous CALB solution in the assayed TSILs ([C_3OHtma] [NTf_2], [C_3CNtma] [NTf_2], [C_4tma][NTf_2], [C_5CNtma] [NTf_2] or [C_6tma] [NTf_2]) and in the presence of both substrates (vinyl propionate and *rac*-1-phenylethanol) at 50 °C and 2 % (v/v) water content. Figure 5A depicts the resulting deactivation profiles, which can be compared with those obtained in hexane. These profiles show that the residual enzyme activity stabilized at a slightly lower level than the initial activity for long incubation periods. Figure 5B shows the evolution of the half-life time of the enzyme, determined by a kinetic analysis of the deactivation profiles (*26*). As can be seen, the increase in hydrophobicity of the main cation chain of the IL produced a great enhancement of the half-life time of the enzyme, which is in agreement with previous results (*20, 21*). At this point, it should be necessary to pointed out how, for the best IL ([C_6tma] [NTf_2]), free CALB showed a half-life time of 239 days at 50 °C and 2 % (v/v) water content. Thus, in non aqueous media, the greater protective effect on enzyme activity afforded by ILs compared with hexane is clear. These results clearly point to the suitability of the most hydrophobic ILs as stabilizing agents, which increase the half-life up to 2000-fold with respect to a classical organic solvent, such as hexane.

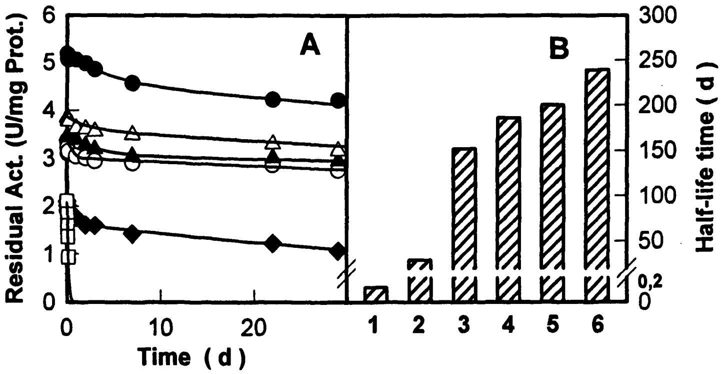

Figure 5. Deactivation profiles (A) and half-life times (B) of CALB at 50 °C in hexane (□, 1) *and different ILs ([C_3OHtma] [NTf_2]* (◆, 2), *[C_3CNtma][NTf_2]* (●, 3), *[C_4tma][NTf_2]* (O, 4), *[C_5CNtma][NTf_2]* (△, 5) *and [C_6tma] [NTf_2])*(▲, 6).

These results show that free CALB is capable of maintaining an active conformation in these non-aqueous environments. The multiphasic nature of the protein molecule during the deactivation process strengthens the suggestion that complex internal events take place during its conformational transition. Therefore, it is reasonable to expect than more than one type of bond must be broken before activity falls off, and this would probably be followed by conformational changes

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of the protein. In this context, the structural changes of CALB, produced by one of the assayed TSILs ([C_4tma][NTf_2]) and hexane after 24 h of incubation were analyzed by CD spectroscopy, and compared with those obtained for the native enzyme in water (see Figure 6A).

As can be seen, the far-UV CD spectrum of native CALB in water was typical of α-helical proteins, with the characteristic double minima at 208 and 222 nm, and the negative band between 205 and 230 nm (*31, 32*). The CDSSTR method for spectrum analysis showed that the secondary structure distribution of the enzyme in water was similar to that reported in the Protein Data Bank (34 % α-helix structure) (*33*) (see Figure 6B). In the case of hexane, the CD spectrum of CALB showed a great increase in its β-strand and unordered secondary structures, which can clearly be correlated with the observed activity loss.

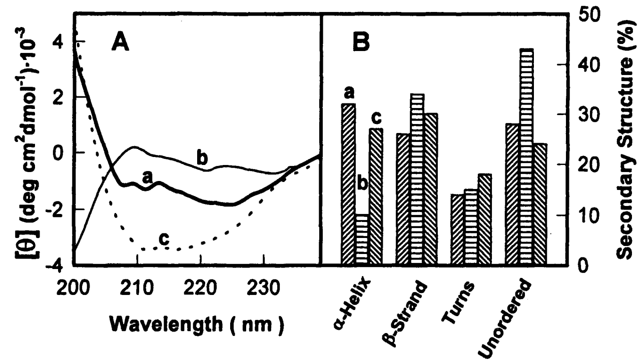

Figure 6. A. Far-UV CD spectra of CALB in (a) water, (b) hexane, (c) [C_4tma] [NTf_2] after 24 h incubation at 50 °C. B. Secondary structure composition of CALB, determined from far-UV CD spectra in different media (See experimental section).

Others authors (*32*) have also described a decrease in the negative CD band of the spectra as a results of thermal unfolding of CALB, relating this spectrum changes with a loss in its helical character. In the case of [C_4tma] [NTf_2], the far-UV CD spectrum of CALB was similar to that observed in water, although there was a slight decrease in α-helix and an increase in β-sheets, while the unordered structure of the enzyme remained practically unchanged with respect to native one. Essentially, the IL maintain a flexible and active conformation of the enzyme, where modifications in the secondary structure might be related with the initial slight decrease in the activity observed in Figure 5A. These results agree with the hypothesis that an aqueous solution of free-enzyme molecules added to the IL phase could be regarded as being included but not dissolved in the medium, the native structure of the protein being preserved, thus providing an adequate hydrophilic microenvironment for the catalytic action (*21, 26, 29*).

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CALB-catalyzed ester synthesis in TSIL-$scCO_2$ biphasic systems.

A continuous biphasic enzymatic reactor was designed, taking into account the excellent properties of ILs to maintain enzymes in an active conformation, as well as the ability of $scCO_2$ to transport hydrophobic substrates and products (see Figure 3) *(25)*. The ability of CALB to catalyze aliphatic ester synthesis in an IL/$scCO_2$ biphasic system, in which the synthetic activity of this lipase was clearly reduced compared with the same IL assayed alone, has also been reported (*9, 26*). Taking into account the biphasic characteristic of the IL/$scCO_2$ system, the mass-transfer phenomena between phases might be considered as a key criterion for the adequate design of a simultaneous biocatalytic and extractive process. In this context, two TSILs ([C_3CNtma][NTf_2] and [C_4tma][NTf_2]) of similar molecular size but differing in the main chain of the cation, were assayed in biphasic systems. To quantify the hydrophobicity of each main chain, Hansen's solubility parameter (δ) (see Table 1) was determined by the method proposed by Kim *et al.* (*34*). In the same way, several model reactions for kinetically-controlled ester synthesis, based on transesterification of different vinyl alkyl esters with alkyl-1-ols, were carried out. In these reactions, the hydrophobicity of both substrates and products was simply determined as a function of the alkyl chain length by the same method (*34*).

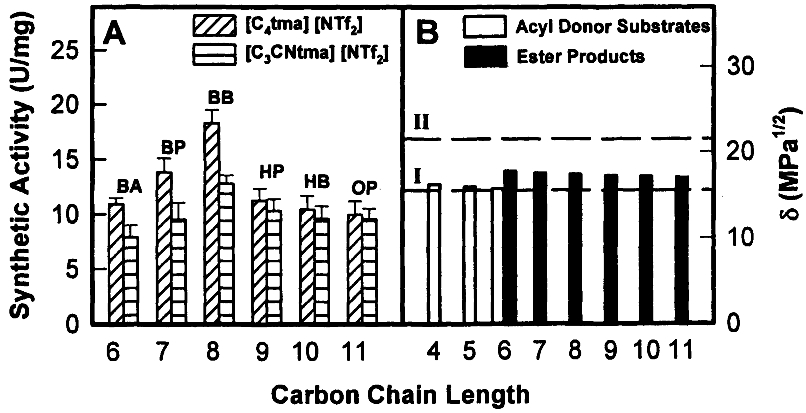

*Figure 7. A. Activity profiles of CALB-[C_4tma][NTf_2] and CALB-[C_3CNtma][NTf_2] systems catalyzing alkyl esters synthesis as a function of the alkyl carbon chain length of the product (butyl acetate, BA; butyl propionate, BP; butyl butyrate, BB; hexyl propionate, HP; hexyl butyrate, HB; and octyl propionate, OP). **B**. Hansen's solubility parameter (δ) of acyl donor substrates and ester products. Dotted lines **I** and **II** indicate the δ-parameter of the main functional side chain of [C_4tma][NTf_2] and [C_3CNtma][NTf_2] cation, respectively.*

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Figure 7A shows the activity profiles of both CALB-[C_4tma][NTf_2] and CALB-[C_3CNtma][NTf_2] systems catalyzing alkyl ester synthesis in $scCO_2$ at 50 °C and 10 MPa, as a function of the alkyl carbon chain length of the synthetic products. As can be seen, in both assayed TSILs, the synthetic activity of CALB showed a bell-curve, with a maximum at an 8-carbon chain length of the product. This fact was also reported for *R. miehei* lipase, where it was explained as an intrinsic characteristic of the enzyme towards substrate size (*35*). However, for all the alkyl esters, it is important to point out how the synthetic activity of CALB-[C_4tma][NTf_2] was higher than that in [C_3CNtma][NTf_2], which is quite the opposite of the results obtained in IL monophasic systems (see Figure 4). Taking into account that in liquid media reactions start with the substrates already dissolved in the IL phase, the lower in activity observed in the IL/$scCO_2$ system might be explained by the mass-transfer limitations (*26*). In biphasic systems, substrates must be transported from the supercritical to the lipase-IL phase, and viceversa in the case of products, their solubility in this liquid phase being the key parameter for controlling the efficiency of the system. To confirm this hypothesis, Figure 7B depicts the δ-parameter of both acyl-donor substrates and ester products as a function of the alkyl carbon chain length. As can be seen, there is a clear agreement between the δ-parameter of both reagents and the main alkyl chain of the cation [C_4tma], which means that the mass-transfer phenomena between this IL and $scCO_2$ phases are better than in the [C_3CNtma][NTf_2] case, thus explaining the observed differences in activity between the IL/$scCO_2$ and pure IL systems. These results mean that a solubility parameter (*e.g.* Hansen's solubility parameter) might be used as a criterion for IL selection, in order to improve the mass-transfer phenomena between ILs and $scCO_2$ phases, and to optimize the efficiency of continuous processes involving enzyme-catalyzed transformation.

Conclusions

Ionic liquids, based on quaternary ammonium cations with different functionalized side chains and the bistriflymide anion, have been shown to act as excellent non-aqueous media for the *Candida antarctica* lipase B-catalyzed kinetic resolution of *rac*-1-phenylethanol. Furthermore, all these TSILs exhibited an important stabilizing effect on the enzyme, increasing the CALB half-life time up to 2000-times with respect to that in hexane. This enhancement in stabilization is related with the increase in the hydrophobicity of the main cation chain, measured by Hansen's solubility parameter. Studies of the secondary structures of CALB by CD spectroscopy showed that the stabilization phenomena were related with maintenance of the native structure of the enzyme.

The efficiency of a continuous biphasic reactor based on CALB-IL-$scCO_2$ systems was dependent on both the specificity of the enzyme towards the catalyzed reaction and the mass-transfer phenomena between ILs and $scCO_2$ non-

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miscible phases. ILs appear to provide an excellent non-aqueous environment for biocatalytic transformations, and their green properties are improved by their ability to over-stabilize enzymes These results clearly show how clean synthetic chemical processes can be designed, thus contributing advancing to the green chemical industry of the near future.

Acknowledgements

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Chapter 17

Ruthenium Catalyzed Asymmetric Hydrogenation of *α*- and *β*-Ketoesters in Room Temperature Ionic Liquids Using Chiral P-Phos Ligand

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Chiral dipyridyl phosphine ligand P-Phos was found to be effective in the Ru-catalyzed asymmetric hydrogenation of α- and β-keto esters in room temperature ionic liquids (RTILs) with high conversions and good to excellent enantioselectivities.

Introduction

Transition-metal catalyzed asymmetric hydrogenation has become one of the most powerful tools for the preparation of optically active compounds in organic synthesis, and high activity and enantioselectivity have been observed using Rh, Ru and Ir complexes with chiral phosphine, phosphite or phosphoramidite ligands (1,2). However, the industrial application of

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asymmetric hydrogenation is still quite limited, partly due to the difficulty in separating and reusing the expensive chiral catalyst. The immobilization of catalyst offers an attractive solution to this problem (3). Recently room temperature ionic liquids (RTILs) such as those based on imidazolium salts have attracted much interest because of their potential as a means to facilitate the immobilization and recycling of the transition metal catalyst (4). A series of prochiral olefins, ketones and imines have been successfully hydrogenated in ionic liquids, and the results were comparable to or even better than those obtained in common organic solvents. In most cases, the organic products could be easily separated via extraction with less polar solvents and the ionic liquid phase containing the active catalyst could be readily reused for several times without significant loss of catalytic activity.

The first asymmetric hydrogenation in ionic liquid was reported in 1995 by Chauvin and coworkers (5). In a biphasic [bmim][PF_6]/*i*PrOH mixture, the use of [Rh(COD)((-)-DIOP)]PF_6 catalyst provided 64% ee in the asymmetric hydrogenation of α-acetamidocinnamic acid. The product retained in the alcohol phase was separated by decantation while the catalyst contained in ionic liquid phase was proved to be reusable.

In 1997, Dupont and coworkers investigated the Ru-catalyzed asymmetric hydrogenation of 2-arylacrylic acids with BINAP ligand in [bmim][BF_4]/*i*PrOH medium (6a). The results obtained were comparable to those achieved in homogeneous organic solvents. The Ru-catalyst could be readily immobilized in ionic liquid and recycled for several times without significant loss of activity and enantioselectivity. The same group also studied the asymmetric hydrogenation of α-acetamidocinnamic acid with Rh(I)-Et-DuPhos as catalyst in ionic liquid/*i*PrOH mixture, and up to 93% enantioselectivity was obtained in [bmim][BF_4]/*i*PrOH medium (6b). The catalyst immobilized in ionic liquid was reused 4 times.

Geresh and coworkers found that asymmetric hydrogenation of enamides with Rh(Me-DuPhos) in the biphasic [bmim][PF_6]/*i*PrOH system could lead to high yields and enantioselectivities which were comparable to those obtained in *i*PrOH (7). Moreover, it was found that the ionic liquid could provide additional stability to the air-sensitive catalyst, enabling all experimental operations including catalyst recycling to be conducted in air without significant loss of enantioselectivity.

Jessop and coworkers described the asymmetric hydrogenation of unsaturated carboxylic acids with Ru-Tol-BINAP as catalyst in wet [bmim][PF_6] followed by the extraction of the product with supercritical carbon dioxide ($ScCO_2$) (8). Due to the insolubility of catalyst in $ScCO_2$, the pure product could be obtained while the catalyst was retained in ionic liquid phase. The recovered catalyst was reused five times with retained activity and even enhanced

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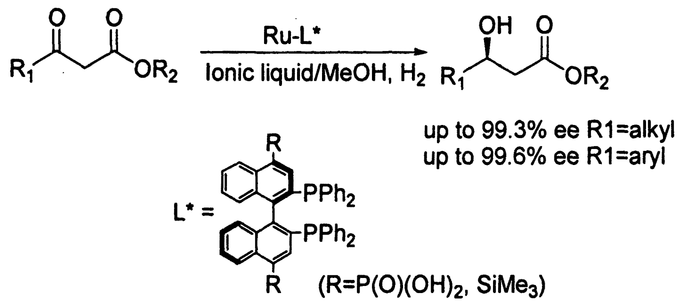
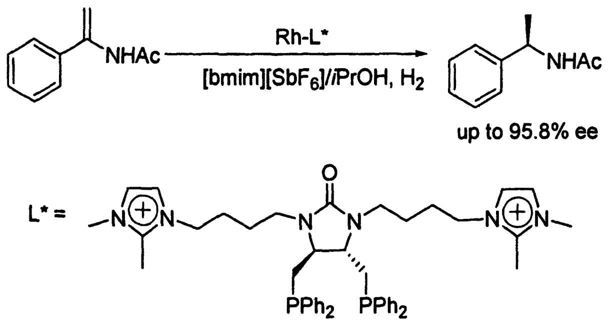
enantioselectivity. This procedure appeared to offer a good solution to the leaching of the catalyst during the extraction.

Lin and coworkers reported the synthesis of modified BINAP ligands, which possessed polar phosphonic acid groups as appendages, and their applications in the asymmetric hydrogenation of β-ketoesters in biphasic ionic liquid/MeOH system (Scheme 1) (9). The ee values attained were higher than those obtained in MeOH. The products were separated via extraction and the immobilized catalyst was recycled for 4 times without significant loss of activity and enantioselectivity. Similar strategy has also been adopted by Lemaire and coworkers in the study of asymmetric hydrogenation in ionic liquids (10).



Scheme 1

Lee and coworkers prepared the new polar bidentate chiral ligand bearing two imidazolium salt tags on the framework for the asymmetric hydrogenation of enamides in ionic liquids (Scheme 2), and found that the Rh-complex could be readily immobilized and reused several times without significant loss of catalytic efficiency (11).



Scheme 2

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The asymmetric hydrogenation of simple ketones has also been realized in ionic liquid (12). Zhu and coworkers found that the Rh-catalyst derived from rhodacarborane [close-1,3-{μ-(η^2-3-CH_2=$CHCH_2CH_2$)}-3-H-3-PPh_3-3,1,2-$RhC_2B_9H_{10}$] and (*R*)-BINAP was very effective for the asymmetric hydrogenation of simple ketones and functionalized ketones in ionic liquids. The results obtained in ionic liquids were better than those in THF. The best result was achieved in a new ionic liquid, $BP^+CB_{10}H_{12}^-$. The catalyst could be readily recovered and reused for 6 times without deterioration of catalytic activity and selectivity.

Pugin et al. recently reported the asymmetric hydrogenation of enamides using Rh-ferrocenyl-diphosphine catalysts in wet ionic liquids with up to >99% ee and more than 10000 turnovers (13). More recently, Leitner and coworkers reported the Ir-catalyzed asymmetric hydrogenation of imines in ionic liquid/$ScCO_2$ biphasic system. They found that the combination of ionic liquids and $ScCO_2$ system could result in efficient activation, tuning and immobilization of the catalyst (14).

We have recently developed a series of pyridyl-diphosphine ligands, namely P-Phos and its derivatives, which have been used in transition metal-catalyzed enantioselective hydrogenation of olefins and ketones to provide the desired products with high yields and excellent ees (15). In this study we found that using ionic liquids as solvent in the Ru(P-Phos)-catalyzed asymmetric hydrogenation of ketoesters gave similarly high enantioselectivity and catalytic activity. The use of ionic liquids simplified the isolation of product and facilitated the recovery of the catalyst.

Asymmetric Hydrogenation of α-Ketoesters

The asymmetric hydrogenation of α-keto esters provides a convenient way to prepare chiral α-hydroxyl esters, which are useful building blocks for biologically active compounds and natural products. High enantioselectivities and good conversions have been achieved by using chiral Ru-phosphine catalysts in common organic solvents (1,2). However, there is no report on the asymmetric hydrogenation of α-keto esters in ionic liquids. To determine whether the catalytic asymmetric hydrogenation of α-keto esters with Ru(P-Phos) catalyst could occur in ionic liquids, we first examined the hydrogenation of methyl pyruvate in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) and 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]). For comparison, we also tested the catalytic performance of the extensively used Ru-BINAP catalyst in ionic liquids. We first attempted the hydrogenation in pure ionic liquids, but the reaction was found to be sluggish with very low conversions (5% in [bmim][BF_4] and 10% in [bmim][PF_6]) after 20 h. In view of the significant co-solvent effect of alcohol in the asymmetric hydrogenation in ionic liquids, we used equal volume of MeOH as a co-solvent. As shown in Table 1, high enantioselectivities were obtained with Ru-P-Phos in

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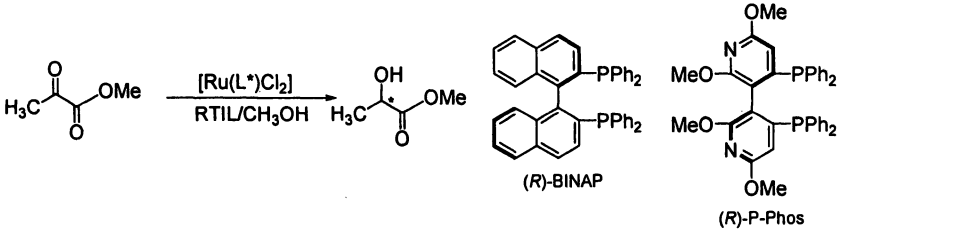
both [bmim][BF_4] and [bmim][PF_6], and the ees were comparable to those achieved in MeOH. The enantioselectivity was insensitive to the nature of the ionic liquids. However, the reaction in [bmim][PF_6] was slower, and only 73% conversion was achieved after 20 h while nearly complete conversion was observed in [bmim][BF_4]. In constrast, lower enantioselectivities were observed in Ru-BINAP catalyzed hydrogenation, though nearly complete conversions were attained in both ionic liquids. With BINAP ligand, the enantioselectivity was quite dependent on the nature of ionic liquids. As shown in Table 1, 81% *ee* was obtained in [bmim][BF_4] while only 55% ee was obtained in [bmim][PF_6]. It was notable that P-Phos worked better than BINAP, which may be attributed to the dipyridyl-backbone of P-Phos (15).

The effect of H_2 pressure was examined. As shown in Table 2, the H_2 pressure had an important effect on the catalytic activity, but the influence on enantioselectivity was negligible (entries 1-6).

Other α-ketoesters were also tested and low to high enantioselectivities were observed (Table 3). Low enantioselectivities and conversions were observed in the hydrogenation of ketopantolactone in both ionic liquids (entries 1-2). Moderate enantioselectivities and low conversions were obtained in the hydrogenation of ethyl 2-oxo-4-phenylbutyrate (entries 3-4). High ee values but low conversions were observed in the hydrogenation of methyl benzoylformate (entries 5-6). The hydrogenation of ethyl benzoylformate only led to low conversions and poor enantioselectivities (entries 7-8).

Table 1. Asymmetric hydrogenation of methyl pyruvate in ionic liquids.[a]



L*	Solvent	Ee (%)[b]	Conv. (%)[c]
(*R*)-P-Phos	[bmim][BF_4]/MeOH	83	95
(*R*)-P-Phos	[bmim][PF_6] /MeOH	86	73
(*R*)-P-Phos	MeOH	88	97
(*R*)-BINAP	[bmim][BF_4] /MeOH	55	98
(*R*)-BINAP	[bmim][PF_6] /MeOH	81	98
(*R*)-BINAP	MeOH	83	90

[a]All reactions were carried out with 1 mol% catalyst under 1000 psi H_2 in a 50:50 mixture of RTIL and MeOH at room temperature for 20 h. [b]The ee values were determined by GC on a Cyclosil-B [J&W scientific] column (30m x 0.25mm x 0.25μm). [c]The conversions were determined by ^1H NMR analyses.

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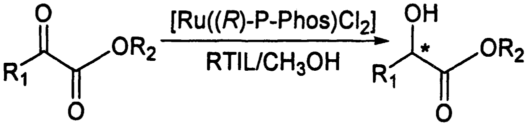
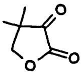
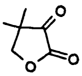
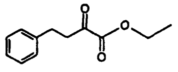
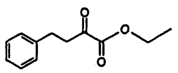
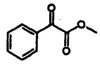
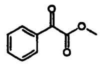
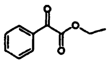
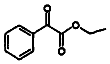
Table 2. Effect of pressure on asymmetric hydrogenation of methyl pyruvate in ionic liquids.[a]

Entry	RTIL	H_2 (psi)	Ee (%)[b]	Conv. (%)[c]
1	$[bmim][BF_4]$	500	83	81
2	$[bmim][PF_6]$	500	86	58
3	$[bmim][BF_4]$	1000	83	95
4	$[bmim][PF_6]$	1000	86	73
5	$[bmim][BF_4]$	1500	83	96
6	$[bmim][PF_6]$	1500	86	75

[a]All reactions were carried out with 1 mol% catalyst in a 50:50 mixture of RTIL and MeOH at room temperature for 20 h. [b]The ee values were determined by GC on a Cyclosil-B [J&W scientific] column (30m x 0.25mm x 0.25μm). [c]The conversions were determined by ^1H NMR analyses.

Table 3. Asymmetric hydrogenation of *α*-ketoesters in ionic liquids.[a]



Entry	Substrate	RTIL	Ee (%)[b]	Conv. (%)[c]
1		$[bmim][BF_4]$	47	34
2		$[bmim][PF_6]$	60	46
3		$[bmim][BF_4]$	74	37
4		$[bmim][PF_6]$	76	63
5		$[bmim][BF_4]$	90	18
6		$[bmim][PF_6]$	93	65
7		$[bmim][BF_4]$	55	26
8		$[bmim][PF_6]$	38	20

[a]All reactions were carried out with 1 mol % catalyst under 1000 psi H_2 in a 50 : 50 mixture of RTIL and methanol at room temperature for 20 h. [b]The ee values were determined by GC on a Cyclosil-B [J&W scientific] column (30m x 0.25mm x 0.25μm). [c]The conversions were determined by ^1H NMR analyses.

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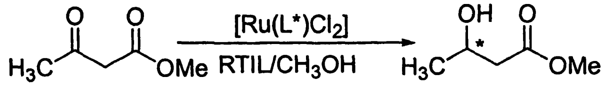
Asymmetric Hydrogenation of *β*-Ketoesters

The asymmetric hydrogenation of β-ketoesters in ionic liquids have been studied, and the results are comparable to those obtained in organic solvents (9,10). However, recycling and reuse of the catalyst in ionic liquids have been problematic due to the leaching and/or instability of the catalyst. In order to overcome these obstacles, the attachment of polar groups to the chiral phosphine ligands has been introduced (9-11). The synthesis of these modified ligands is tedious, and much extra synthetic effort is required. It is desirable to develop an efficient hydrogenation process in ionic liquids with easily accessible ligands. In this pursuit we examined the capability of $[Ru((R)\text{-P-Phos})Cl_2]$ in the asymmetric hydrogenation of β-ketoesters in ionic liquids (Table 4). The hydrogenation of methyl acetoacetate in a mixture of equal volume of ionic liquid ($[bmim][BF_4]$ or $[bmim][PF_6]$) and MeOH was first examined. After stirring at room temperature for 20 h, the reaction led to complete conversion and up to >99% ee. As shown in Table 4, the same reaction was also conducted using (*R*)-BINAP as ligand in both ionic liquids. Again excellent conversions and enantioselectivites were achieved in both ionic liquids.

The effect of H_2 pressure was examined, and the results were summarized in Table 5. The H_2 pressure had significant influence on the rate of reaction (entries 1-6). Under 500 psi H_2, the conversions in both ionic liquids were only 23% and 49%, respectively. However, when the pressure was increased to 1000 psi or higher, nearly complete conversions were achieved in both ionic liquids.

The results of the asymmetric hydrogenation of other *β*-ketoesters are summarised in Table 6. High enantioselectivities (97% to 99%) and high conversions (92% to >99%) were obtained for methyl acetoacetate, ethyl acetoacetate and *tert*-butyl acetoacetate (entries 1-4). It should be pointed out that these results are comparable to those obtained in organic solvents. However, when R^1 was switched to electronegative groups, both the enantioselectivity and

Table 4. Asymmetric hydrogenation of methyl acetoacetate in ionic liquids.[a]



L*	RTIL	Ee (%)[b]	Conv. (%)[c]
(*R*)-P-Phos	$[bmim][BF_4]$	>99	>99
(*R*)-P-Phos	$[bmim][PF_6]$	98	>99
(*R*)-BINAP	$[bmim][BF_4]$	>99	>99
(*R*)-BINAP	$[bmim][PF_6]$	>99	>99

[a] All reactions were carried out with 1 mol % catalyst under 1000 psi H_2 in a 50:50 mixture of RTIL and MeOH at room temperature for 20 h. [b]The ee values were determined by GC on a Supelco γ-Dex 225 column. [c]The conversions were determined by ^1H NMR analyses.

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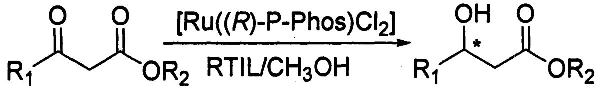
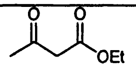
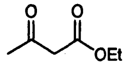
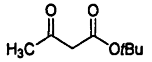
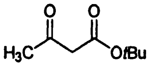
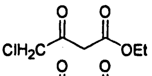
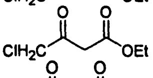
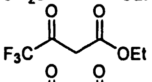
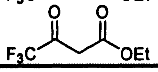
Table 5. Effect of pressure on asymmetric hydrogenation of methyl acetoacetate in ionic liquids.[a]

Entry	RTIL	H_2 (psi)	Ee (%)[b]	Conv. (%)[c]
1	[bmim][BF_4]	500	94	23
2	[bmim][PF_6]	500	90	49
3	[bmim][BF_4]	1000	>99	>99
4	[bmim][PF_6]	1000	98	>99
5	[bmim][BF_4]	1500	>99	>99
6	[bmim][PF_6]	1500	99	>99

[a]All reactions were carried out with 1 mol% catalyst in a 50:50 mixture of RTIL and MeOH at room temperature for 20 h. [b]The ee values were determined by GC on a Supelco γ-Dex 225 column. [c]The conversions were determined by [1]H NMR analyses.

Table 6. Asymmetric hydrogenation of *β*-ketoesters in ionic liquids.[a]



Entry	Substrate	RTIL	Ee (%)[b]	Conv. (%)[c]
1		[bmim][BF_4]	>99	>99
2		[bmim][PF_6]	97	>99
3		[bmim][BF_4]	>99	86
4		[bmim][PF_6]	>99	92
5		[bmim][BF_4]	54	91
6		[bmim][PF_6]	58	93
7		[bmim][BF_4]	50	21
8		[bmim][PF_6]	21	78

[a]All reactions were carried out with 1 mol% catalyst under 1000 psi H_2 in a 50:50 mixture of RTIL and MeOH at room temperature for 20 h. [b]The ee values were determined by GC on a Supelco γ-Dex 225 column. [c]The conversions were determined by [1]H NMR analyses.

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the conversion declined (entries 5-8). The Ru(P-Phos) catalyst showed higher activity in [bmim][PF_6] but gave better enantioselectivity in [bmim][BF_4].

The recyclability of the Ru-P-Phos catalyst in RTIL was examined using methyl acetoacetate as the model substrate. Upon completion of the reaction, the methanol was evaporated in vacuo, and the product was extracted with degassed hexane. The RTIL phase was washed twice with hexane. The combined extracts were used for analysis. The RTIL phase was recharged with methyl acetoacetate and MeOH, and then subjected to hydrogenation again under the same conditions. As shown in Table 7, the Ru(P-Phos) could be reused and recycled in both ionic liquids, but the results differ considerably. In [bmim][BF_4]/MeOH, the level of enantioselectivity could be reasonably maintained for 9 runs, but the activity deteriorated from the second run, and the subsequent runs led to a significant drop in activity. However, in the case of [bmim][PF_6], good activity and excellent enantioselectivity were retained in the first five runs of the hydrogenation reactions.

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Table 7. Recycling and reuse of Ru((*R*)-P-Phos) catalyst for the asymmetric hydrogenation of methyl actoacetate in ionic liquids.[a]

Entry	RTIL	Run	Ee (%)[b]	Conv. (%)[c]
1	[bmim][BF_4]	1	>99	>99
2		2	98	87
3		3	97	78
4		4	96	71
5		5	95	62
6		6	95	56
7		7	93	52
8		8	94	33
9		9	94	39
10	[bmim][PF_6]	1	98	>99
11		2	98	99
12		3	97	96
13		4	97	96
14		5	96	93
15		6	96	86
16		7	96	78
17		8	94	57
18		9	94	49

[a]All the reactions were carried out with 1 mol% catalyst under 1000 psi H_2 in a 50:50 mixture of RTIL and MeOH at room temperature for 20 h. [b]The ee values were determined by GC on a Supelco γ-Dex 225 column. [c]The conversions were determined by ^{1}H NMR analyses.

In summary, we have examined the use of Ru(P-Phos) catalyst in the asymmetric hydrogenation of α- and β-ketoesters in RTILs with high conversions and ee values (up to >99% ee). The catalyst was recycled and reused several times with reasonable retention of activity and enantioselectivity.

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Chapter 18

Organocatalyzed Asymmetric Michael Reaction in Ionic Liquids–Carbon Dioxide

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The asymmetric Michael reaction catalysed by the chiral amines quinine, quinidine, L-proline, (-)-sparteine, (-)-ephedrine and the quinidine derivative QD4 was studied in ionic liquids and by dissolving CO_2 using ethyl 2-cyclopentanone carboxylate and methyl vinyl ketone as model substrates. While the observed yields in the ionic liquids based on the methylimidazolium cation were similar to the ones obtained in toluene, the enantioselectivities were considerably lower. However, the dissolution of CO_2 in the ionic liquid provokes a considerable increase on the enantioselectivities.

Introduction

The development of asymmetric methodologies based on organic catalysis has been an extremely active area during the last years *(1)*. Some of the catalytic systems already developed, as for example the asymmetric aldol reaction catalyzed by proline, are quite sensitive to the solvent system used. In many cases the chemical immobilization of the catalyst also leads to some erosion of the enantioselectivity. Room temperature ionic liquids (ILs), apart of being a new and peculiar media which has been applied in different areas *(2)*, are also a very appealing reaction media in organic chemistry with special focus in

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organometallic catalysis, organocatalysis and biocatalysis.*(3)*. Due to being non-volatile, and the possibility to modulate the solubility properties of the ILs relative to common organic solvents, water, catalysts, organic reactants and products by appropriate combination of the cation and anion, allows a very simple, robust and efficient method for catalyst reuse just by immobilization of the catalyst in the IL under homogeneous conditions. The success of this approach needs firstly that the catalyst has a strong affinity to the IL phase in opposition to the solvent used, including *sc*CO_2 *(4)* or membrane technology *(5)* to remove the reaction products. Secondly, it is extremely crucial for the catalyst to be effective in the IL reaction medium, with special emphasis in the case of asymmetric catalysis. During the last years it has been demonstrated that ILs are in fact a serious alternative reaction media in a considerable range of catalytic reactions *(3)* where in many examples were observed similar enantioselectivites to the ones in traditional organic solvents.

The catalytic addition of 1,3-dicarbonyl compounds to conjugate acceptors, the classic Michael reaction, is an important organic synthetic transformation allowing for stereoselective C-C bond formation in a high atom economy fashion. There are various efficient reported catalyzed systems based on the use of chiral metal catalysts *(6)*. In opposition, apart of phase-transfer catalysis *(7)*, the organocatalysis has been considerable less successful *(1, 6)* in the Michael reaction.

For the last years this laboratory has been involved in the development of new ionic liquids based on the imidazolium *(8)* and guanidinium (9) cations and their application in selective transport as bulk and supported liquid membranes between two organic *(10)* and aqueous phases *(11)*, separation by pervaporation *(12)* and efficient immobilization of photochromic probes *(13)*. Another application of the ILs has been their use in organic transformations were the IL presents some advantage to the use of traditional organic solvents such as a promoting media for nucleophilic reactions *(14)* and in non-asymmetric catalysis in which the catalyst is efficiently immobilized in the IL, as in the tetrahydropyranylation of alcohols catalysed by *p*-toluenesulphonic acid pyridinium *p*-toluenesulphonate, and triphenylphosphine hydrobromide *(15)*, Baylis-Hillman reaction promoted by DABCO *(16)*, in the epoxidation of cyclooctene catalyzed by dioxo-molybdenum and cyclopentadienyl-molybdenum complexes *(17)* and in the C-H Insertion of α-diazo-α-phosphono-acetamides catalysed by $Rh_2(OAc)_4$ *(18)*. Additionally, we explored the use of ILs as an efficient reaction and immobilization media in asymmetric catalysis such as in the comparision between *sc*CO_2, organic solvents and ILs for enzymatic acylation *(19)*, enantioselective addition of alkynes to imines catalysed by Cu(I)-bis(oxazoline) complex *(20)* and in the Sharpless asymmetric dihydroxylation of olefins using ILs as a co-solvent *(21)* and solvent followed by product recovery using *sc*CO2 *(22)*. In line with the above studies, we focused the potential use of Ils in the asymmetric Michael reaction, assuming that the ionic and coordination properties of ionic liquids, would eventually

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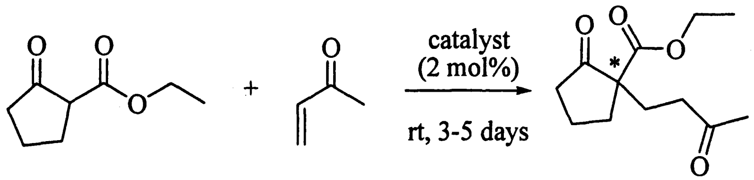
facilitate the reaction due to the expected formation of polar reaction intermediates catalysed by chiral organocatalysis.

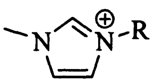
Results and Discussion

The potential use of ILs as reaction medium in the Michael reaction was studied using ethyl 2-cyclopentanone carboxylate **1** and methyl vinyl ketone **2** as model substrates (Scheme 1). Several chiral amines were tested as potential catalysts in line with reported examples in organic solvents, namely alkaloids (23) and proline (24). Several ionic liquids based on the imidazolium and guanidinium cations (Figure 1) were tested and compared with toluene, a conventional solvent commonly used for this reaction (Table 1). It seems that the nature of the solvent has a negligible effect on the chemical yield. The only exception is proline in which the lower yield in [bmim]PF_6 is probably due to lower solubility of the catalyst in the reaction medium (entries 8 and 9). In opposition, the solvent has a considerable effect in the enantioselectivity for all the catalyst tested . In all cases tested the ee are lower in the ionic liquid than in toluene. Additionally, increasing solvent polarity leads to decreasing on enantiomeric excesses (entries 2-5 and 15-18; [C_8mim]PF_6 > [C_8mim]BF_4 > [bmim]PF_6 > [C_2OHmim]PF_6).



1 **2** **3**

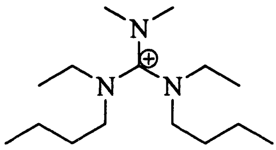
Scheme 1. General Michael reaction tested.



[bmim] R = *n*-butyl

[C_8mim] R = *n*-octyl

[C_2OHmim] R = CH_2CH_2OH



[$(be)_2$dmg]

Figure 1. Cation structure of the ionic liquids tested

In Ionic Liquids in Organic Synthesis; Malhotra, S.;
ACS Symposium Series; American Chemical Society: Washington, DC, 2007.

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Table 1. Observed yields and enantiomeric excesses (ee) of the Michael adduct 3.[a]

Entry	Solvent	Catalyst	Time (days)	Yield[b] (%)	ee[c] (%)
1	Toluene	Quinine	5	89	56 (-)
2	[bmim]PF_6	Quinine	5	91	10 (-)
3	[C_8mim]PF_6	Quinine	5	90	25 (-)
4	[C_8mim]BF_4	Quinine	5	93	14 (-)
5	[C_2OHmim]PF_6	Quinine	5	86	4 (-)
6	Toluene	Quinidine	4	86	47 (+)
7	[bmim]PF_6	Quinidine	4	89	22 (+)
8	Toluene	L-Proline	4	34	7 (-)
9	[bmim]PF_6	L-Proline	4	26	2 (-)
10	Toluene	(-)-Sparteine	4	87	4 (+)
11	[bmim]PF_6	(-)-Sparteine	4	79	0
12	Toluene	(-)-Ephedrine	4	91	0
13	[bmim]PF_6	(-)-Ephedrine	4	95	0
14	Toluene	QD4[d]	4	95	18 (-)
15	[bmim]PF_6	QD4[d]	4	90	0
16	[C_8mim]PF_6	QD4[d]	5	95	5 (-)
17	[C_8mim]BF_4	QD4[d]	5	93	4 (-)
18	[C_2OHmim]PF_6	QD4[d]	5	84	2 (-)

[a] Reaction conditions: 1 (1 mmol), 2 (1 mmol), solvent (250 μL), catalyst (0.02 mmol), rt. [b] Yield of purified product isolated by flash chromatography. [c] enantiomeric excess determined by HPLC of the corresponding dinitrophenylhydrazone (DNPH) derivative; the signal (+) and (-) corresponds to the observed optical rotation for **3**. [d] QD4 (structure given bellow) is a quinidine derivative *(25)*.

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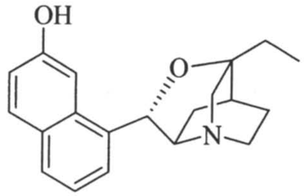

QD4

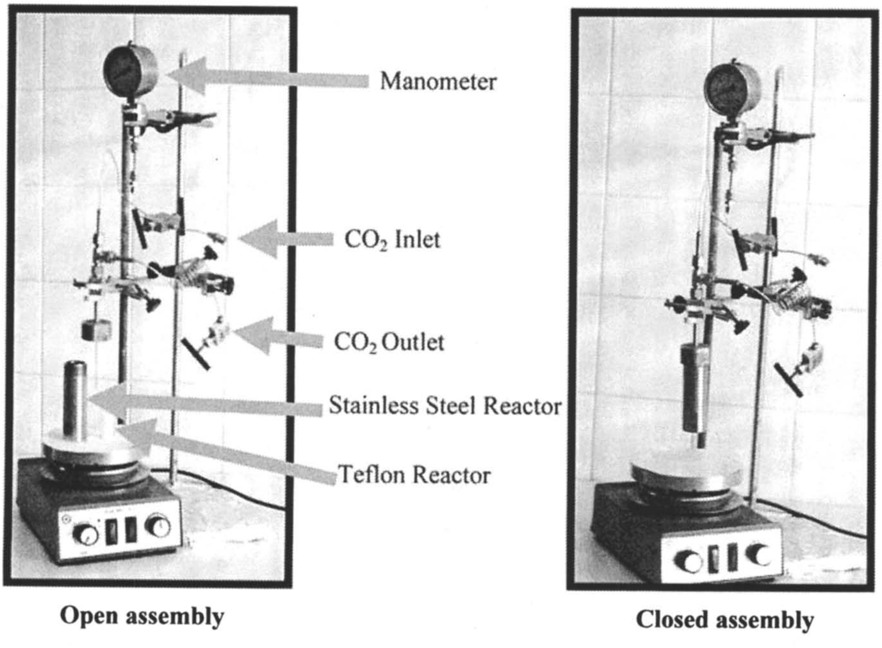

Figure 2. Apparatus used to perform the reaction containing CO_2 dissolved in the reaction medium.

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Based on this observation, and knowing that CO_2 is apolar and quite soluble in ionic liquids *(26),* we were prompted to retest the reaction using a CO_2 atmosphere at different pressures, expecting that the dissolved gas would decrease the polarity of the ionic liquids, hence improving the optical yields. These experiments were performed using the apparatus shown in Figure 2. in which the reagents were poured inside the teflon vial, introduced inside the stainless steel reactor and then filled with moderate pressures of CO_2.

Table 2 presents the results obtained using CO_2 pressure and quinine as catalyst. The same general reaction conditions were used as in the previous examples. In case of toluene using lower pressure of CO_2 was observed a drastic erosion on the yields and in the enantioselectivity when compared to toluene alone (entry 1, yield 41% *vs* 89% and ee of 35 % *vs* 56%). Interestingly, for the ionic liquids tested we observed some reduction on the yields but a considerable increase in the enantiomeric excess just by using only 9 bars CO_2 (entry 2, for [bmim]PF_6, yield 66% *vs* 91% and ee of 21 % *vs* 10%; entry 4, for [C_8mim]PF_6, yield 85% *vs* 90% and ee of 30 % *vs* 25%). Using 30 bar of CO_2 allows an increase of the enantiomeric excess (entries 4 and 6; ee 30% (9 bar), 35% (30 bar)). The erosion of the yields in the presence of CO_2 dissolved in organic solvent or ionic liquid is probably due to the occurrence of some reversible reaction between the tertiary amine functional group of the catalyst quinine with the CO_2*(27)*, which reduces the amount of active catalyst present in the reaction media. Regarding to the enantioselectivity, the decrease of the enantioselectivity by changing the solvent from toluene to the IL is probably due to the occurrence of competitive interactions between the polar reactive intermediate and the IL throught the formation of C-H hydrogen bonds and polar interactions. When CO_2 is dissolved in the IL, is expected that it undergoes competitive interaction

Table 2. Observed yields and enantiomeric excesses (ee) of the Michael adduct 3 in the presence of CO_2 using quinine as catalyst.[a]

Entry	Solvent	pCO_2 (bar)	Time (days)	Yield[b] (%)	ee[c] (%)
1	Toluene	9	3	41(89)[d]	35(56)[d]
2	[bmim]PF_6	9	3	66(91)[d]	21(10)[d]
3	[(be)$_2$dmg]PF_6	9	3	90	22
4	[C_8mim]PF_6	9	3	85(90)[d]	30(25)[d]
5	[C_8mim]PF_6	20	3	64	29
6	[C_8mim]PF_6	30	3	76	35

[a] Reaction conditions: 1 (1 mmol), 2 (1 mmol), solvent (250 μL), quinine (0.02 mmol), rt, inside the teflon reactor presented in Figure 2 in which was applied CO_2 atmosphere. [b] Yield of purified product isolated by flash chromatography. [c] enantiomeric excess of the (-) enantiomer determined by HPLC of the corresponding dinitrophenylhydrazone (DNPH) derivative. [d] In brackets are presented the results obtained in the absence of CO_2.

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with the ionic liquid allowing an overall reduction of IL-reactive intermediate interactions.

In conclusion, the lower enantioselectivity observed for the organocatalysed Michael reaction using the model substrates **1** and **2** in the ionic liquids, as already observed for other transformations such as in the Aldol reaction and 1,4-conjugate addition catalysed by proline and derivatives *(28)*, again shows that ionic liquids present some limitations. However, this study clearly demonstrates that this problem can be eventually circunvented by dissolving CO_2 in the ionic liquid which appears a very simple method and easy way for fine tuning the properties of the ionic liquids. This phenomenon is expected to be applied in the increase of enantioselectivites in other asymmetric reactions.

Acknowledgements

We thank Fundação para a Ciência e Tecnologia and FEDER (Ref. POCTI/EQU/35437/1999 and Ref. PRAXIS XXI/BD/18286/98) for financial support.

Experimental Section

General Remarks: Commercially supplied reagents were used as supplied. Toluene was freshly distilled over calcium hydride. All reactions were performed in oven-dried glassware under an atmosphere of argon. All ILs tested were prepared in this laboratory. The ILs based on the [bmim] and [C_8mim] were prepared according to reported procedures *(29)* and the ILs containing the [C_2OHmim] and the tetra-alkyl-dimethylguanidinium [dmg] cations were reported previously from this laboratory *(8, 9, 30)*. The quinidine derivative **QD4** was prepared following the reported procedure *(25)*. Flash chromatography was carried out on silica gel 60 M from MN (Ref. 815381). Reaction mixtures were analysed by TLC using ALUGRAM® SIL G/UV_{254} from MN (Ref. 818133, silica gel 60). Visualisation of TLC spots was effected using UV, solution of phosphomolybdic acid or I_2. Infrared spectra (IR) were recorded on a Mattson Instruments model Satellite FTIR as thinly dispersed films. High and low resolution mass spectra (EI, FAB) were carried out by mass spectrometry service of University of Santiago de Compostela (Spain). NMR spectra were recorded in a Brucker AMX 400 using $CDCl_3$ as solvent and $(CH_3)_4Si$ (^1H) as internal standard. All coupling constants are expressed in Hz. Optical activities were measured on an Optical activity, Mod. AA-1000, with a 5 cm cell. The enantiomer excess was determined by HPLC analysis using Merck & Hitachi components L-600A, L-4250, T-6300, D-6000 on a Chiralcel OD column at 25 °C.

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Preparation of racemic 3: Racemic **3** was prepared according to a reported procedure *(31)*: To a stirred mixture of $FeCl_3.6H_2O$ (5 mg, 0.02 mmol) and ethyl 2-cyclopentanone carboxylate **1** (300 μL, 2.0 mmol) at room temperature, was added methyl vinyl ketone **2** (180 μL, 2.0 mmol). After 24 hours, the reaction mixture was purified by flash chromatography (eluent: *n*-hexane/ethyl acetate 4:1) to give **3** (381 mg, 83 %) as an clear oil, spectral data identical to the ones reported *(32)*.

General procedure for the organocatalysed Michael Reaction (Tables 1 and 2): Ethyl 2-cyclopentanone carboxylate **1** (150 μL, 1.0 mmol) and the organocatalyst (0.02 mmol) was added to the solvent (toluene or ionic liquid) followed by the addition of methyl vinyl ketone **2** (90 μL, 1.0 mmol) and the reaction mixture was stirred at room temperature for (3-5 days, see tables). The reaction mixture was purified by flash chromatography (eluent: *n*-hexane/ethyl acetate 4:1) to give **3** as an clear oil, spectral data identical to the ones obtained for the racemic sample and reported *(32)*. The reactions performed under CO_2 pressure, were done inside the teflon reactor shown in Figure 2, which were then placed inside the stainless steeel reactor, closed and pressurized under CO_2 atmosphere.

For the determination of enantiomeric excesses the product **3** (100 mg) was transformed into the corresponding dinitrophenylhydrazone (DNPH) derivative using a acid (concentrated H_2SO_4; 0.4 to 0.5 mL) solution of 2,4-dinitrophenylhydrazine (200 to 250 mg) in methanol (5 mL). The precipitate and the mother liquor were purified by flash chromatography (eluent: *n*-hexane/ethyl acetate 1:1) to give the DNPH derivative. The enantiomeric excesses were determined using a Chiralcel OD column at 25 °C (eluent: *n*-hexane/ethanol 40:60), λ_{max} = 372 nm, t_R = 67 and 110 min. The possibility of occurrence of some racemization during the preparation of the DNPH derivative *(33)* was not found to occur because the observed ees by HPLC were consistent with the measured optical purity of the Michael product **3**.

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Chapter 19

Enantiomerically Pure Thiazolinium and Imidazolium Low Melting Point Salts Prepared from α-Aminoacids

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In this chapter are described two new series of chiral ionic liquids, both being obtained from α-aminoacids, taking advantage of enantiomeric purity as well as polyfunctionality of the starting materials. Two strategies are disclosed, in which the cationic unit is obtained either from the aminoacid moiety or the side-chain.

In the increasing field of organic chemistry in ionic liquids, a novel fascinating aspect consists in the study of the potential of these neoteric solvents in asymmetric synthesis. Literature in this topic has been reviewed recently (*1*). In addition to the evaluation of known stoichiometric and catalytic asymmetric reactions in these new media, a promising research area consists in the design of new chiral ionic solvents, whose high degree of organization could possibly afford significant transfer of chirality (*1*). For example, interesting shift effects have been reported (*2*), and the first asymmetric Baylis-Hillman reaction in a chiral ionic liquid was disclosed by Vo-Thanh in 2004 (*3*). Recently, Armstrong reported the first use of chiral ionic liquids as stationary phase in GC (*4*).

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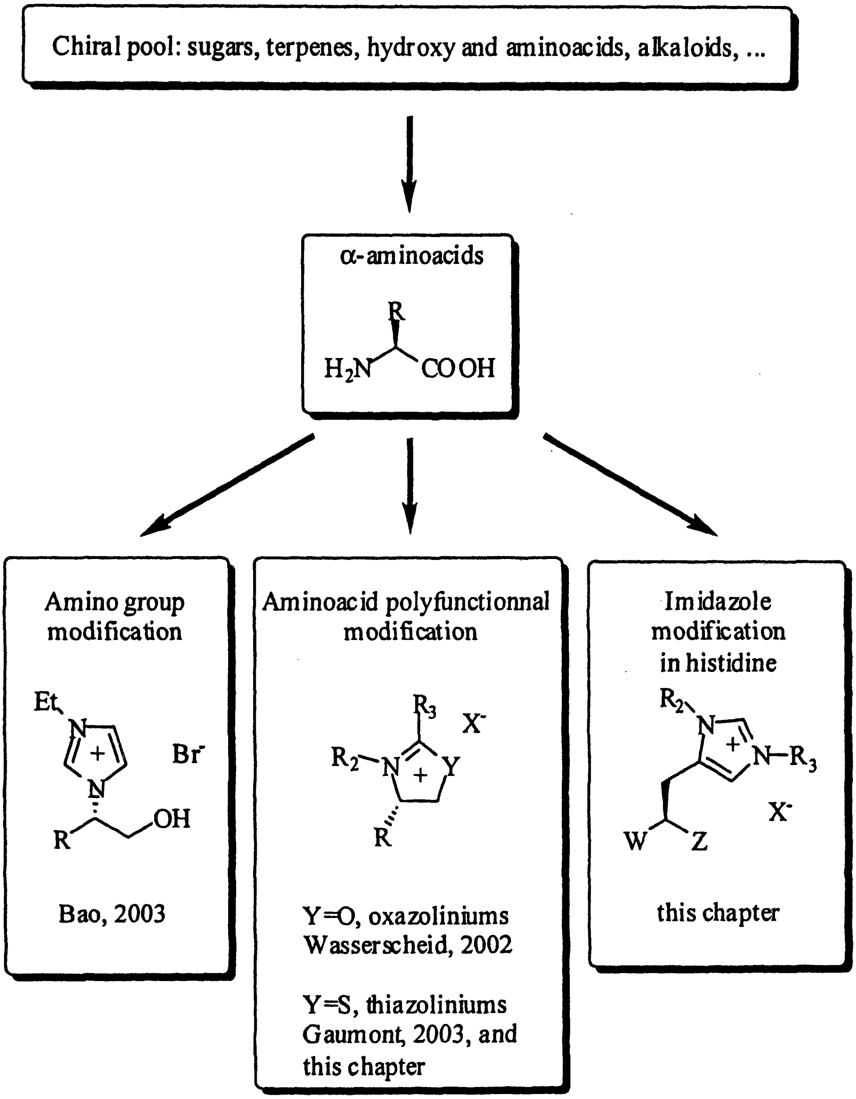

Figure 1. Chiral ionic liquids derived from aminoacids.

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So far reported chiral ionic liquids possess either a chiral anion (*5*), or more frequently an asymmetric unit in the cationic part. Generally obtained from the chiral pool, this chiral element can be central (*2, 6, 7, 8,* 9, *10, 11, 12, 13*), axial (*14*) or even planar (*15*).

Due to their low cost and availability, we thought α-aminoacids to be starting materials of choice for the construction of various chiral ionic solvents. Indeed, using this class of chiral compounds also allows structural modifications, thanks to the variety of side chains. Retrosynthetically, one can imagine at least three approaches, which could afford the desired targets (Figure 1).

Bao's strategy relies on the structural construction of the imidazolium ring starting from the amino group of different aminoacids (*9*). Oxazolinium and thiazolinium salts were prepared, respectively, by Wasserscheid (*8*) and Gaumont (*2*) by functional arrangement of (S) valine derivatives. New results in the series of thiazolinium salts are discussed in the following part of this chapter. Finally, a new set of chiral ionic liquids was designed and synthesized starting from (*S*)-histidine, a naturally occurring aminoacid in which an imidazole ring is present in the R side chain. These new compounds are described in the second part of the chapter.

Chiral Thiazolinium Salts from Enantiopure Aminoacids: Design, Synthesis and Applications

Design and Syntheses of 2-Substituted 2-Thiazolinium Salts

The first family of chiral ionic liquids (CILs) was selected taking into account economical as well as chemical aspects. First, the chirality of the salt should arise from a low cost and readily available precursor (i.e. a compound derived from the chiral pool). Second, the synthesis of the chiral cation should be straightforward in multi-gram scale. Third, the salts should have a low melting point (< 100°C) and good thermal and chemical stabilities. For all these reasons, we focused our attention on the thiazolinium cations, cations that have never been used before for the design of ionic liquids. These salts are easily accessible from enantiopure aminoalcohols through a thiazoline intermediate as depicted in figure 2.

The thiazoline precursors were prepared starting from low cost aminoalcohols and easily accessible dithioester as sulfur source (*16*). Thioacylation of the suitable enantiopure aminoalcohol, under basic conditions leads to a variety of chiral hydroxythioamides in good yields (Scheme 1).

Cyclisation of the thioamide was realized using mesylchloride in the presence of triethylamine leading to the expected thiazolines in good yields (Scheme 2).

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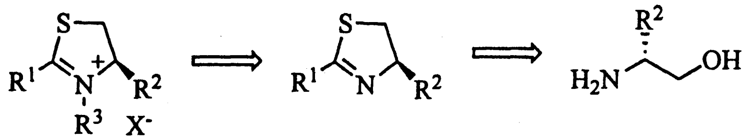
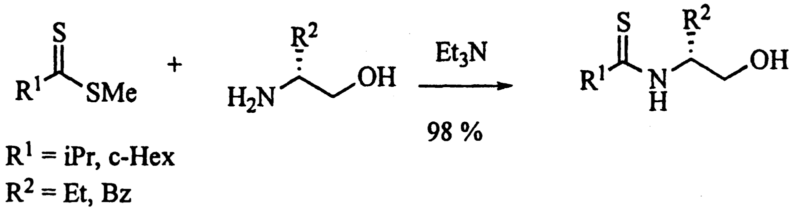
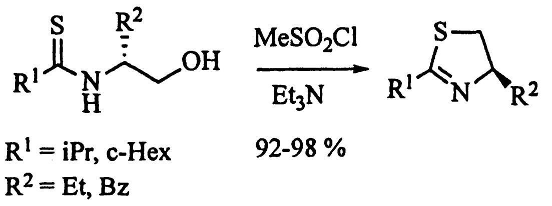


Figure 2. Retrosynthetic approach to thiazolinium salts



ieme 1. Synthesis of thioamide from a dithioester and a chiral aminoalcohol



Scheme 2. Synthesis of chiral thiazolines

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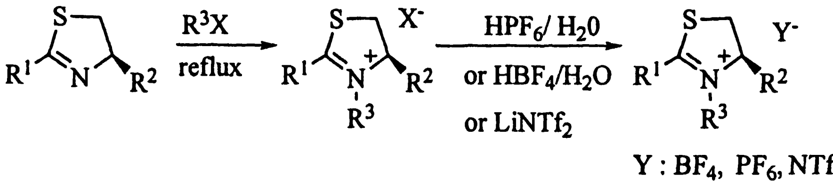
Alkylation of the thiazoline precursors was performed neat upon refluxing with an excess of alkyl halide. The reaction proceeded cleanly to afford the corresponding iodide salt in good yield with butyl iodide (69%); however, with the less reactive dodecyl iodide a lower yield of the desired salt was obtained (31%). Nevertheless, the unreacted precursor can be recovered and then reused. Anion exchange using the appropriate inorganic acid (HPF_6, HBF_4) or the lithium salt of bistriflimide ($LiNTf_2$) yielded the corresponding new salts (Scheme 3).



Scheme 3. Synthesis of thiazolinium salts

A high structural diversity in thiazolinium salts is accessible using this methodology by readily modification of one or more of the thiazolinium substituents, R^1, R^2, and R^3, coming respectively from the dithioester, the aminoalcohol and the alkylating agent (Figure 3).

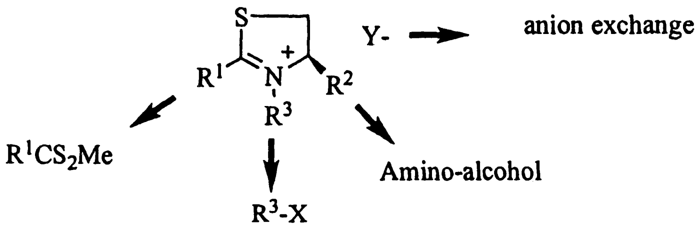


Figure 3. Structural diversity in thiazolinium salts

All the new chiral salts having a BF_4, PF_6 or NTf_2 anion are soluble in polar organic solvents such as dichloromethane, chloroform, and acetonitrile, slightly soluble in ether, toluene or water. They show good stability under aqueous basic and acidic conditions, contrarily to their oxazolinium analogues (*8*).

The thermal decomposition of some of these salts was studied by thermogravimetry analysis (TGA). No decomposition was observed at temperature lower than 170 °C.

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The melting point of the salts, measured by DSC, depends both on the combination of the R^1, R^2, R^3 thiazolinium substituents and on the nature of the counteranion. As shown in Table 1, for a given thiazolinium cation (R^2 = Et, R^3 = Bu), the melting point decreases from the iodide to the tetrafluoroborate anion (137 to 111°C, entries 1 to 3) as already observed for imidazolium derivatives (*8, 9*). With the bis-trifluorosulfonimide anion (entry 4), the salt is a viscous liquid at room temperature, having a glass transition temperature at -68 °C. Interestingly, the salts having a dodecyl group on R^3 position always have a lower melting point (106 to 38°C entries 6, 8 and 10) showing the importance of the alkyl chain length. With the bis-trifluorosulfonimide anion (entry 7), a glass transition temperature was measured at -67°C.

Table 1. Yields and physical properties of chiral thiazolinium salts

Entry	R^1	R^2	R^3	*Anion*	*Yield*[a]	*mp (°C) or gT*[b]	α_D *(c 1, acetone)*
1	iPr	Et	Bu	I	62	137	-40,7
2	iPr	Et	Bu	PF_6	50	136	-35,6
3	iPr	Et	Bu	BF_4	50	111	-32,5
4	iPr	Et	Bu	NTf_2	51	-68[b]	-29,5
5	Cy	Et	Bu	I	91	104	-
6	iPr	Et	Dod	PF_6	23	42	-36,7
7	iPr	Et	Dod	NTf_2	23	-67[b]	-36,7
8	iPr	Et	Dod	I	28	38	-38,8
9	iPr	Bz	Bu	I	63	172	+33
10	iPr	Bz	Dod	I	25	106	-
11	iPr	Bz	Bu	PF_6	43	165	+34
12	iPr	Bz	Bu	NTf_2	46	-	-

[a] Overall yields starting from the dithioester

[b] Glass transition temperature

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Application of thiazolinium salts in chiral recognition with racemic Mosher's acid salt

To evaluate the ability of these salts to form chiral interactions with racemic substrates, we have attempted to detect diastereomeric interactions between the enantiopure thiazolinium salts and the racemic silver Mosher's acid salt. Both salts having a poor solubility in apolar solvent, the anion exchange was performed in acetonitrile. After removal of silver iodide by filtration, the solvent was evaporated. The new salt was dissolved in d6-benzene and ^{19}F NMR spectra were recorded (Figure 4). A downfield shift of 1 ppm together with the splitting

of the CF_3 signal (ΔδJ = 1Hz) account for the formation of the diastereomeric salts (Figure 4, a). Addition of a co-solvent (water) had a major influence on the extent of signal splitting (ΔδJ = 11Hz), as already observed for an ammonium salt (*8*).

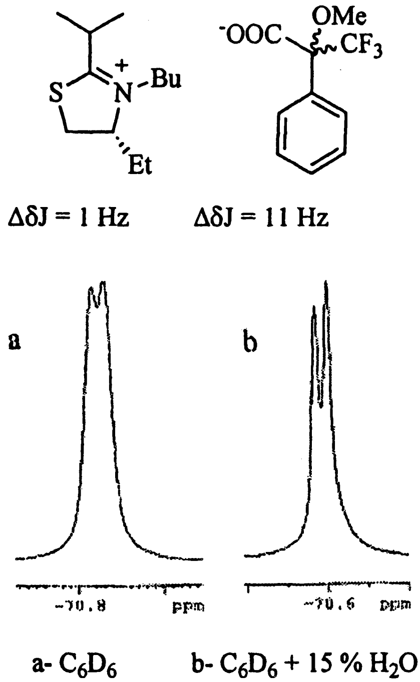

Figure 4. ^{19}*F NMR spectrum of diastereomeric 2-ethyl-2-thiazolinium salts*

To improve the interactions, we investigated the role of the substituents on the thiazolinium salts. Replacing the R^1 (isopropyl group) by a phenyl or a cyclohexyl group proved to have no benefit. However, the replacement of the R^2 group (ethyl) by a benzyl one, proved to have a great influence on the chemical shift difference. An important extend in the signal splitting (from 1 to 15,5 Hz) was observed, and this, in the absence of water (Figure 5). This result can be explained by a Π-stacking interaction between the two aromatic groups.

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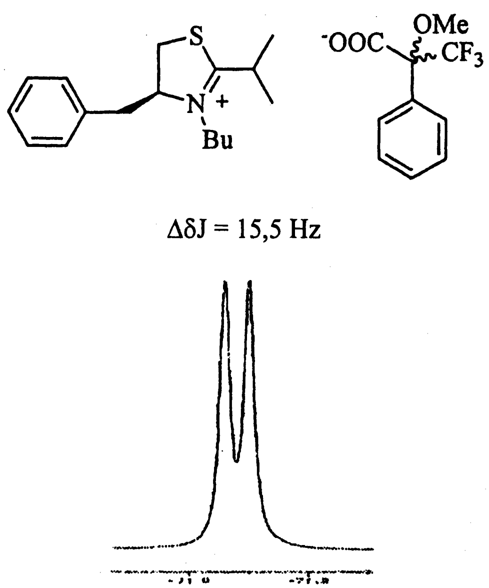

Figure 5. ^{19}F NMR spectrum of diastereomeric 2-benzyl-2-thiazolinium salts in d_6-benzene

Other functional modifications are currently under study in order to improve the use of these new salts in the field of shift reagents.

Chiral Imidazolium Salts from (*S*)-Histidine: Design, Synthesis and Physicochemical Properties

In order to benefit from the presence of the two different functions of an aminoacid for further chemical transformations, one can also consider the construction of the organic salt moiety on the side chain of the aminoacid rather than using the amine and/or acid function. Histidine, which possesses an imidazole ring in the side chain, is particularly attractive: simple alkylation of the two nitrogens of the imidazole ring should provide a chiral bifunctional imidazolium salt (figure 6). Usual aminoacid chemistry can then be performed on the ionic liquid aminoacid, in order to obtain the desired functions.

Dissymmetric substitution of the two imidazolium nitrogens is usually required in order to obtain low melting point and low viscosity in simple (i.e.

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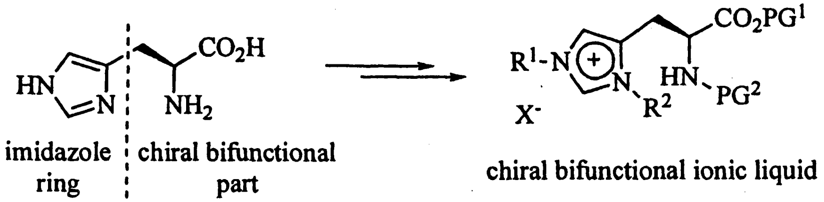
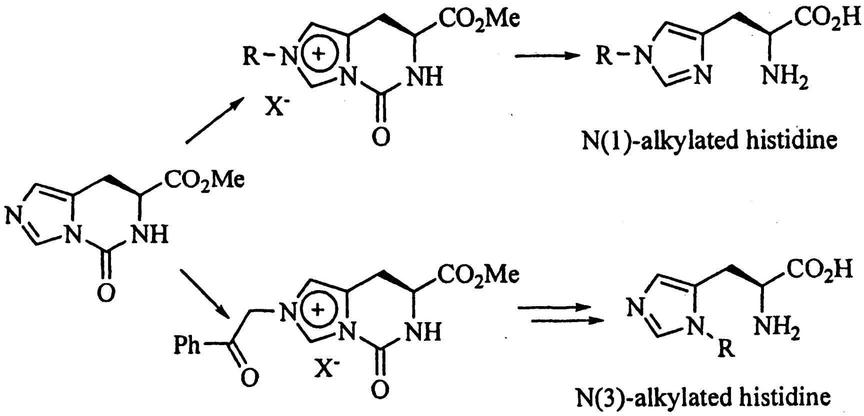


Figure 6. Chiral bifunctional imidazolium salts from histidine

without substituent in position 4 and 5) 1,3-dialkylimidazolium salts (*17*). Selective alkylation of both imidazole nitrogen atoms, while leaving the amine nitrogen untouched, is therefore highly desirable.

Simultaneous protection of the amine and the 3 position of the imidazole ring can be conveniently accomplished *via* an intermediate cyclic urea, which can be subsequently alkylated at N (1) with an alkyl halide (Scheme 4). This strategy affords, after deprotection, either 1-alkylated histidines (direct alkylation) (*18*) or 3-alkylated histidines, *via* the temporary protection of N (1) by a phenacyl group and subsequent alkylation (*19*). More interestingly, the opening of the urea by an alcohol gives directly the corresponding carbamate, eliminating the need of subsequent protection of the amine function (*19*).

As reported by Cohen (*18*), treatment of the histidine methyl ester dihydrochloride with carbonyldiimidazole in DMF afforded the cyclic urea as a



Scheme 4. Selective alkylation of histidine derivatives via a cyclic urea

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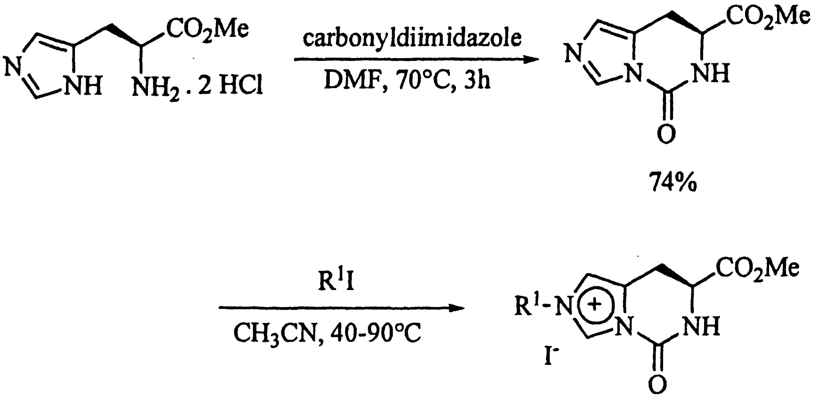
white crystalline solid in a good yield. Alkylation with methyl iodide in acetonitrile proceeded smoothly to give the corresponding iodide salt in high yield: the less reactive propyl iodide required higher temperature, and afforded a lower yield of the desired salt (Scheme 5).

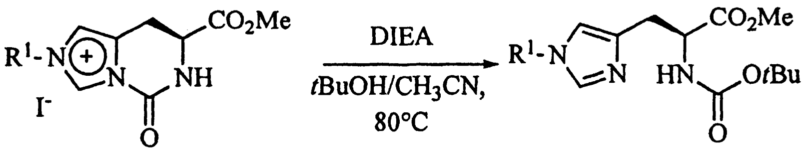


R^1 = Me, 97 %
R^1 = Pr, 67 %

Scheme 5. Construction of cyclic ureas starting from histidines

The cyclic ureas were then opened by *tert*-butanol in the presence of diisopropylethylamine, to give the Boc-protected N(1)-alkylated histidine methyl esters (Scheme 6).

A direct synthesis of Boc-protected 1-alkylhistidine from Boc-protected histidine was recently described (*20*): however initial protection of the aminoacid as the Boc-derivative is required.



R^1 = Me, 69%
R^1 = Pr, 49%

Scheme 6. Opening of charged cyclic ureas by tert-butanol.

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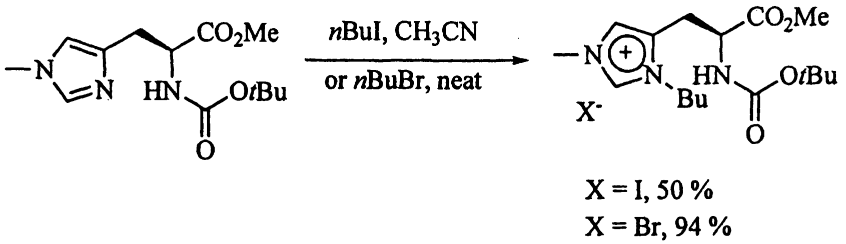
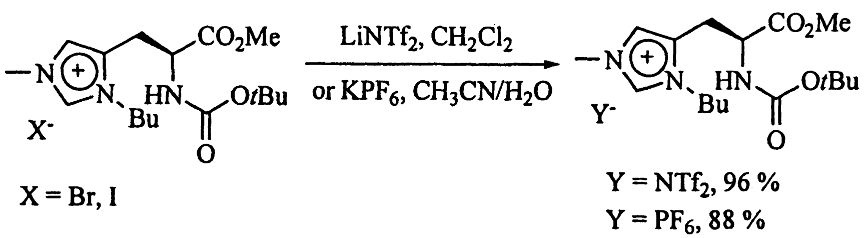
Subsequent alkylation at N (3) was effected on the methylated histidine derivative with butyl iodide in acetonitrile or, more conveniently, in butyl bromide without the need of an added solvent, owing to the solubility of the substrate in *n*-butyl bromide (Scheme 7).



Scheme 7. Alkylation of 1-methylhistidine derivatives

The resulting hygroscopic halide salts were immediately engaged in a metathesis reaction with lithium bistriflimide or potassium hexafluorophosphate (Scheme 8).



Scheme 8. Anion metathesis

Both salts are waxy white solids with low melting points (40°C for NTf_2), insoluble in water, alkanes or ether but soluble in most other organic solvents. Thermogravimetry analysis of the bis-triflimide salt showed thermal stability up to 170°C.

Functional modification of the protected chiral imidazolium salt aminoacid, aiming at the preparation of a range of chiral task specific ionic liquids, is currently under study. For example, chemoselective reduction of the methyl ester can be carried out with lithium borohydride to afford the corresponding protected aminoalcohol in 63% yield, allowing access to β-aminoalcohol derivatives such as oxazolines and thiazolines, among others.

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Conclusion and Prospects

In summary, we have designed two new families of chiral ionic liquids using natural and renewable starting materials derived from the chiral pool, i.e. aminoacids. Two methodologies were developed taking advantages of the structure of the aminoacids. The organic cations were constructed either from the functional groups (amino and carboxylic acid functions) or from the side chain (imidazole ring of histidine) leading respectively to chiral thiazolinium and imidazolium based ionic liquids.

Thiazolinium salts were easily prepared in 4 steps starting from a dithioester with reasonable to good yields in multigram scale. These salts are water tolerant and stable under acidic and basic aqueous conditions. By judicious choice of the nature of the anion and the structure of the cation, salts having a low melting point are obtained. Diastereomeric interactions between a thiazolinium salt and the racemic Mosher's acid silver salt have been demonstrated by ^{19}F NMR, which makes these new ionic liquids potential candidates for enantioselective reactions.

Regarding imidazolium chiral salts, we were delighted to be able to obtain low melting point salts in which both nitrogen atoms of the imidazole ring were selectively alkylated. The reaction sequence is convergent and efficient enough to give access to substantial amount of the desired chiral ionic liquids. This new series of chiral compounds is now the starting point for the construction of various task specific ionic liquids, in which the amino and carboxy functions will be modified for various purposes.

The chiral ionic liquids highlighted in this chapter and others developed by several groups are only at the beginning of what promises to be an exciting field of research. Due to their peculiar properties and to their ease of synthesis, these chiral ionic liquids should give a renewal in the chemistry of chiral solvents and chiral reagents.

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Chapter 20

New Cations for Ionic Liquids, Including Chiral Adjuncts with Phosphate and Sulfonylimide Anions

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A series of new ionic liquids has been prepared and investigated incorporating a variety of ammonium and polyammonium cationic components. These include several topographies, including linear arrays (strings) with stereogenic sites along the array, and both pyrrolidinium and pyridinium species bearing ether and chiral adjuncts. The associated anions for these systems include the (environmentally friendlier) phosphate and bis(trifluoromethyl)sulfonylimide species. Physical and chemical characteristics of the anhydrous ionic liquids have been investigated.

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Introduction

General

Prior efforts of this laboratory have been concerned with the preparation and investigation of several varieties of ionic liquids (*1-7*). In the present effort our particular concern is with the preparation and investigation of *chiral* ionic liquids, those bearing at least one stereogenic site within the covalent structure of the cationic portion.

Rationale

While the potential utility of ionic liquids in general has begun to be realized, that of *chiral* ionic liquids has yet to be established firmly. We can envision several areas of application for such materials, given that they can be prepared in suitable quantity economically and in an environmentally friendly (green) manner. These potential applications include:

- The exhibition of enantiomeric selectivity in reactions using ionic liquids as the reaction media.
- The exhibition of enantiomeric selectivity in electrochemical processes.
- The exhibition of enantiomeric selectivity in separation processes.

Our efforts reported here are concerned with the discovery and exploitation of chiral ionic liquids for these purposes.

Requirements

In general, the requirements for *chiral* ionic liquids to be of value for applications as noted above, in addition to their exhibiting the required enantiomeric selectivity, are quite similar to those of ionic liquids in general. That is, they must be of relatively low viscosity at the appropriate temperature for operation. In addition, they must reasonably be available from precursors without the need for enantiomeric separations and convertible to the proper salt form without compromising the chirality. Finally, for them to be of use as more than a laboratory curiosity, they must exhibit "green" characteristics, including stability of both cation and anion thermally and hydrolytically, and involve minimal energy expense in the preparation of themselves and their precursors. Ideally, the chiral material should be a readily available species from biorenewable sources.

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Anion Focus

With the previously mentioned considerations in mind, activities of the current effort have been directed toward the use of several anions to be associated with the chiral ionic liquids. Overall, as the cationic portions of ionic liquids are generally formed by reactions of amines with organic halides or tosylates, ionic liquids generated bearing those anions (halides or tosylates) involve a minimum of preparative effort and thus have a desirable characteristic.

However, at times halide or tosylate anions may not desirable for other required properties of the ionic liquid. Phosphate (PO_4^{3-}) is an anion with which ammonium ions can often form ionic liquids (*1-7*) and does not degrade to undesirable substances in aqueous media or under thermal stress. As such, ionic liquids bearing phosphate anions constitute fundamentally "green" materials. The major difficulty with such materials is in their preparation, the conditions of which can often lead to racemization or degradation of the cationic component. Alternatives to the halides and phosphates, not readily hydrolyzable in aqueous media and with reasonable thermal stability are the bis(trifluoromethyl)sulfonylimides [NTf_2^-], readily prepared from the halide salts and generally liquids of relatively low viscosity (*8, 9*).

It is with these anion species (halides, tosylates, phosphates and [NTf_2]$^-$, that our search for stable, unreactive and facilely generated chiral ionic liquids is directed.

Results and Discussion

Our initial efforts toward the preparation and investigation of chiral ionic liquids has been concerned with those bearing the chiral 2,3-dihydroxypropyl-group. While the *racemic* 2,3-dihydroxy-1-chloropropane was used to establish appropriate reaction conditions for preparation of ionic liquids, the chiral reagents were ultimately used to generate directly the chiral ionic liquid species.

Both the (*R*)- and the (*S*)-2,3-dihydroxy-1-chloropropane were used in reaction with 4-(dimethylamino)pyridine (acetonitrile solvent, overnight reaction) to generate the enantiomeric chiral ionic liquid *chlorides* as shown in Figure 1. Determination of water content using the Karl-Fisher titration technique indicated less than 1% residual water. The enantiomeric chloride salts exhibited identical ^1H and ^{13}C NMR spectra, in accord with their proposed structures.

The resultant (*R*)- chloride salt was converted to the (*R*)- [NTf_2^-] salt by the standard procedure (*8, 9*), the latter was dried under vacuum (<1% water) and found to exhibit ^1H and ^{13}C NMR spectra corresponding to that of the (*R*)-chloride salt with the exception that there was present in the ^{13}C spectrum a quartet at δ 119.45 owing to the presence of the CF_3-group in the anion. The [NTf_2^-] salt thus formed exhibited $[\alpha]_D = -13.5°$ at 25°C and 0.01 *M* (ethanol).

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In a similar manner 1,4-diazabicyclo[2.2.2]octane (dabco) was allowed to react with 2,3-dihydroxy-1-chloropropane. Using one equivalent of the (*R*)-material, a liquid chloride salt (m.p. 30°C) was isolated (Figure 2) that exhibited $[\alpha]_D = -28.3°$ at 25°C and 0.01 *M* (ethanol). This salt was similarly converted to the $[NTf_2^-]$ salt that exhibited $[\alpha]_D = -4.29°$ at 25°C and 0.01 *M* (ethanol). Using two equivalents of the (*S*)- starting material, a diadduct liquid dichloride salt could be isolated (Figure 2) that exhibited $[\alpha]_D = 30.0°$ at 25°C and 0.01 *M* (ethanol).

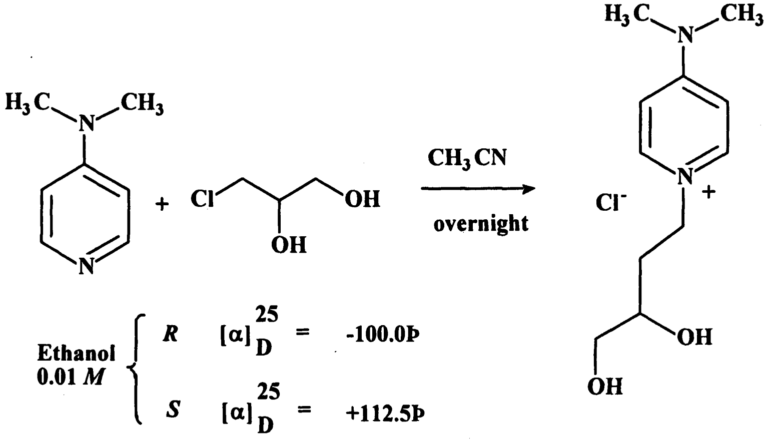

Figure 1. Reaction of enantiomers of 3-chloro-1,2-propanediol with 4-(dimethylamino)pyridine

Finally, the (*S*)-3-chloro-1,2-propanediol was used to generate a chiral ionic liquid by reaction with *N*-methylpyrrolidine in the standard manner. The resultant chloride salt (Figure 3) exhibited $[\alpha]_D = 22.4°$ at 25°C and 0.01 *M* (ethanol).

One of the requirements for chiral ionic liquids to be truly "green" was noted to be the ready availability of the chiral portion, preferably in sizable quantity from biorenewable sources. This has led us to a consideration of carbohydrate derived materials for use in the cationic portion of the salts. As noted in other efforts from this laboratory concerned with the construction of ammonium salts, the primary hydroxyl sites of carbohydrates and carbohydrate derived materials provide for selective and facile conversion to such species (*10-12*).

Initial efforts resulting in the preparation of a chiral ionic liquid in this laboratory (*13*) involved a biologically derived material, albeit not a carbohydrate. (*S*)-Mailc acid (biological sources) is readily converted to (*S*)-1,3,4-butanetriol and further to 2,2-dimethyl-4-(2'-chloroethyl)1,3-dioxolane. Subsequent reaction with dabco in ethyl acetate medium resulted in the formation of the room temperature ionic liquid as shown in Figure 4. Although highly viscous,

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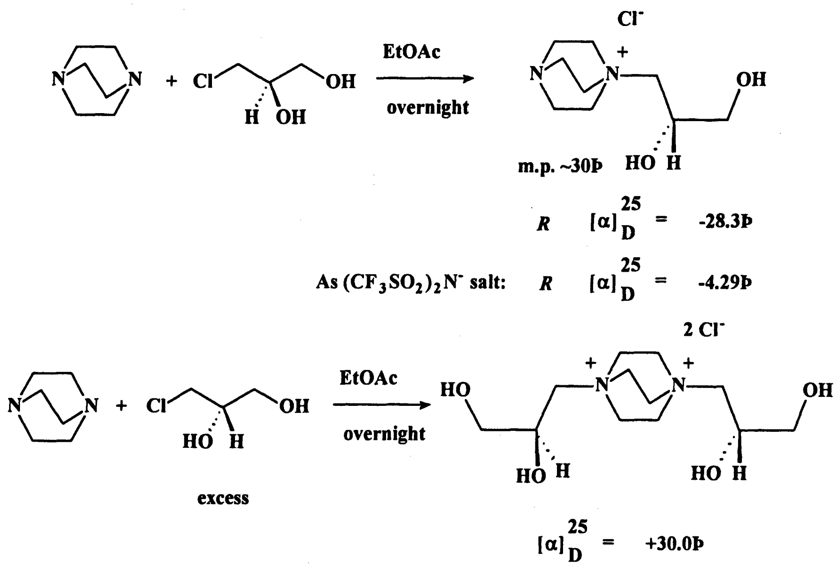

Figure 2. Chiral ionic liquids from 3-chloro-1,2-propanediol with dabco

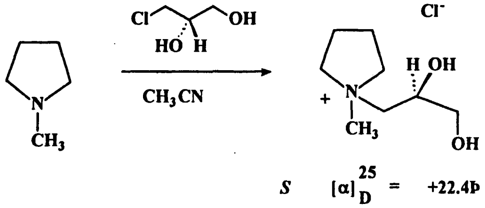

Figure 3. Preparation of a chiral ionic liquid based on N*-methylpyrrolidine*

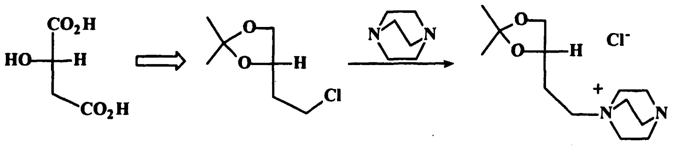

*Figure 4. A chiral ionic liquid from (*S*)-malic acid*

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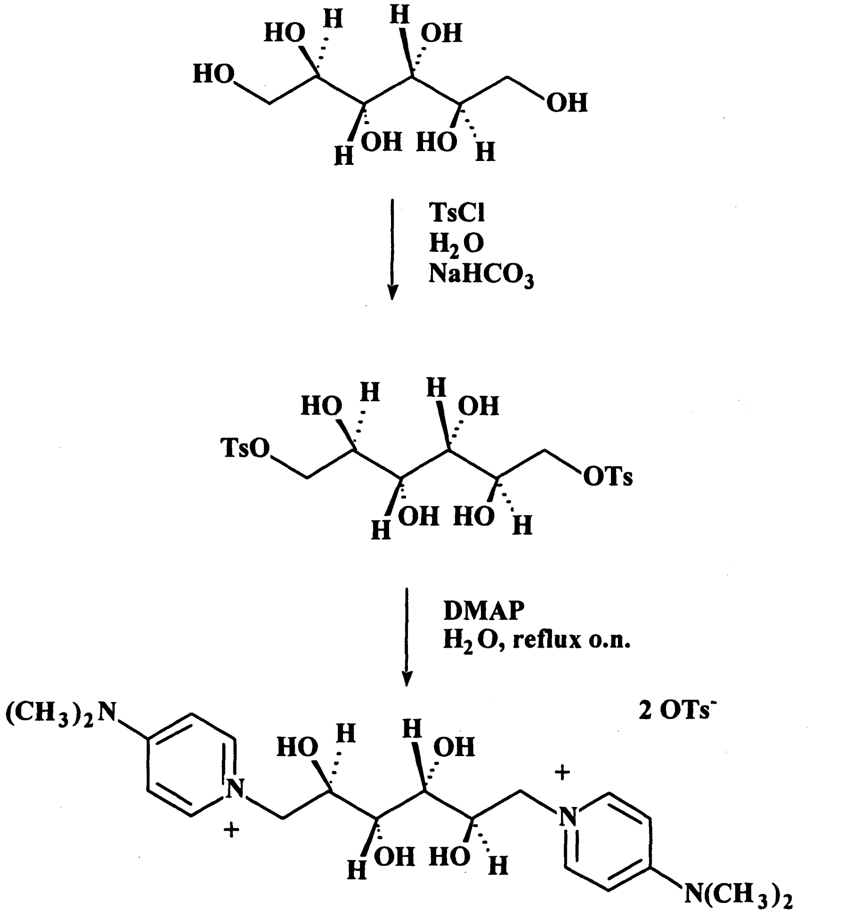

Figure 5. Preparation of a chiral ionic liquid from D-mannitol

the resultant material is liquid and remains so through various attempts at crystallization.

Primary hydroxyl sites of carbohydrates may be selectively tosylated (*14*) (compared to other hydroxyl sites) and the primary carbon site thereby rendered subject to selective substitution by tertiary amines (*10-12*). Two carbohydrate derived species that are particularly intriguing for preparation of "green" ionic liquids are D-mannitol and methyl D-glucopyranoside. In addition to being chiral, each is readily available from biological sources at reasonable cost and bears primary hydroxyl groups that are available for facile transformation into quaternary ammonium sites.

In this light we undertook the preparation of chiral ionic liquids using each of these materials. D-Mannitol was treated according to a modified tosylation

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procedure developed in this laboratory (*15*) (tosyl chloride, aqueous sodium bicarbonate) to generate the 1,6-ditosylate derivative (Figure 5). The resultant ditosylate, without isolation, was treated with two equivalent amounts of 4-(dimethylamino)pyridine (overnight heating) from which could be isolated in 59% yield the liquid bis-quaternary ammonium salt in the tosylate form which exhibited ^{1}H and ^{13}C NMR spectra in accord with the proposed structure and $[\alpha]_D$ = 25.2° at 25°C and 0.01 *M* (ethanol). Other salts have been prepared using this backbone (*e.g.* through reaction of the 1,6-ditosylate of D-mannitol with 1-hexadecylazonia-4-aza-bicyclo[2.2.2]octane chloride) that were not liquid at room temperature but are currently under investigation for conversion into alternative anion forms.

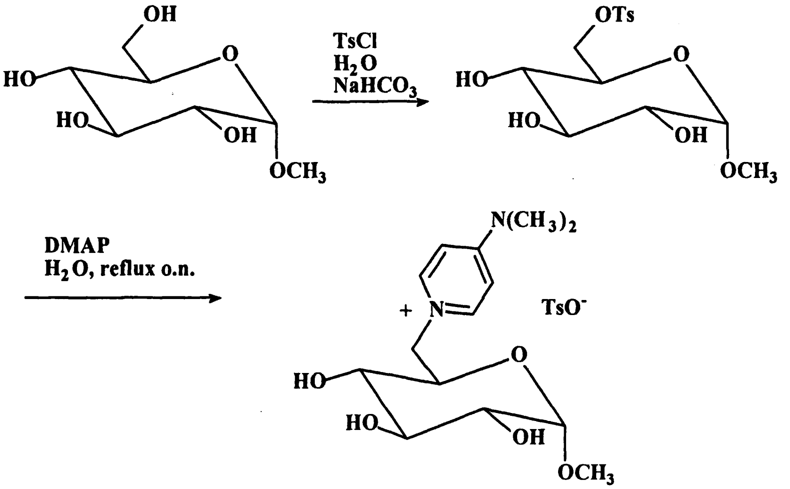

Figure 6. Chiral ionic liquid from methyl D-glucopyranoside

In a similar manner the readily available methyl D-glucopyranoside was converted to the tosylate ester at the 6-position hydroxyl group and subsequently was treated with 4-(dimethylamino)pyridine to generate in 65% isolable yield the chiral ionic liquid in the tosylate form as shown in Figure 6. Again, the product salt exhibited ^{1}H and ^{13}C NMR spectra in accord with the prpoposed structure and $[\alpha]_D$ = 55.3° at 25°C and 0.01 *M* (ethanol).

The facile conditions for the preparation of these materials and the ready availability of the starting materials provides such chiral ionic liquids with a significant potential for practical utility. The continuing efforts of this laboratory are concerned with the development of additional chiral cationic species from biological sources for use to this end, as well as the modification of the associated anions for the development of a library of chiral ionic liquids with a wide selection of chemical and physical characteristics.

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Chapter 21

Tailoring Adsorption–Desorption Properties of Hydroamination Catalysts with Ionic Liquids

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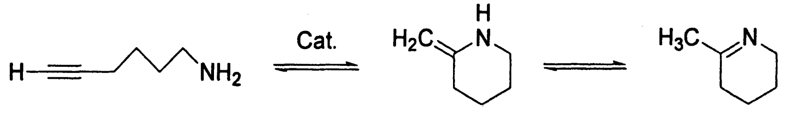
Abstract: Highly active and selective homogeneous catalysts are known for atom efficient syntheses of aromatic and aliphatic amines from alkenes and alkynes. We have shown that catalytically active metal cations (such as Zn^{2+}) can be incorporated in zeolites and display a higher activity due to the simultaneous presence of Lewis acid sites and Brønsted acidic hydroxyl groups. Surprisingly high catalytic activities were also observed for molecular catalysts in two phase systems where the catalyst was dissolved in an ionic liquid. The high activity is caused by a high solubility of the reactants in the catalyst phase whereas the products are hardly soluble. Here we report on well-tailored catalysts combining both approaches.

Introduction

The direct addition of an amine N-H to a non-activated alkene or alkyne (hydroamination) has found rapidly increasing interest of the scientific community in recent years (1,2). Studying the intramolecular reaction of 6-aminohex-1-yne *via* 2-methylenepiperidine to 2-methyl-1,2-dehydropiperidine (Equation 1), we had identified Lewis acidic transition metal complexes, such as



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In Ionic Liquids in Organic Synthesis; Malhotra, S.;
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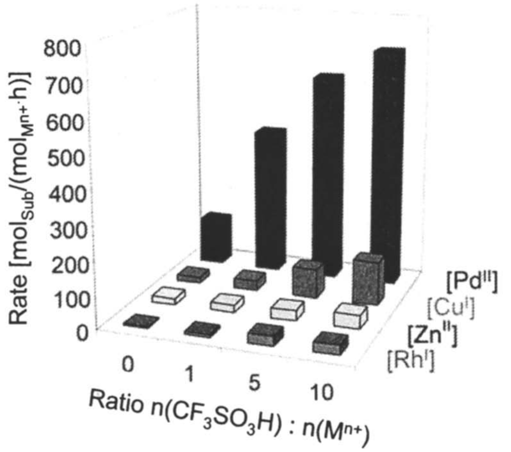

Figure 1. Catalytic activity of [Pd(Triphos)](CF_3SO_3)$_2$, [Cu(CH_3CN)$_4$]PF_6, Zn(CF_3SO_3)$_2$ and [Rh(NOR)$_2$]ClO_4 in the cyclisation of 6-aminohex-1-yne. The Brønsted acid CF_3SO_3H was added as co-catalyst in the ratios indicated.

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[Pd(Triphos)](CF_3SO_3)$_2$ (Triphos = *bis*-(2-diphenylphosphino-ethyl)-phenylphosphine), [Cu(CH_3CN)$_4$]PF_6, Zn(CF_3SO_3)$_2$, [Rh(NOR)$_2$]ClO_4 (NOR = Bicyclo[2.2.1]hepta-2,5-diene) as suitable catalysts for the addition of amines to alkynes. For each of these catalysts, the rate of reaction could be increased significantly by the addition of a Brønsted acid to the reaction mixture (Figure 1).

This is consistent with a mechanism based on the coordination of the alkyne group to the metal centre (Lewis acidic function), which enables nucleophilic attack of the amine group (Figure 2) (3). The cleavage of the metal-carbon bond of the intermediate 2-ammonio-alkenyl-complex formed, as well as subsequent isomerisation of the enamine formed by the hydroamination reaction to the corresponding imine, can be accelerated in the presence of protons as co-catalyst (Brønsted acidic function).

Hydroamination has the potential to become an industrially applicable reaction as it constitutes a new and direct approach to nitrogen containing molecules starting from readily available alkenes and alkynes. However, for operation in a continuous process the homogeneous catalyst will have to be immobilized (4). Here, we compare three different approaches, i.e. classic heterogenization on a solid surface, immobilization of the active complex in a second liquid phase and supporting a catalyst solution as thin film of liquid on a solid (Figure 3).

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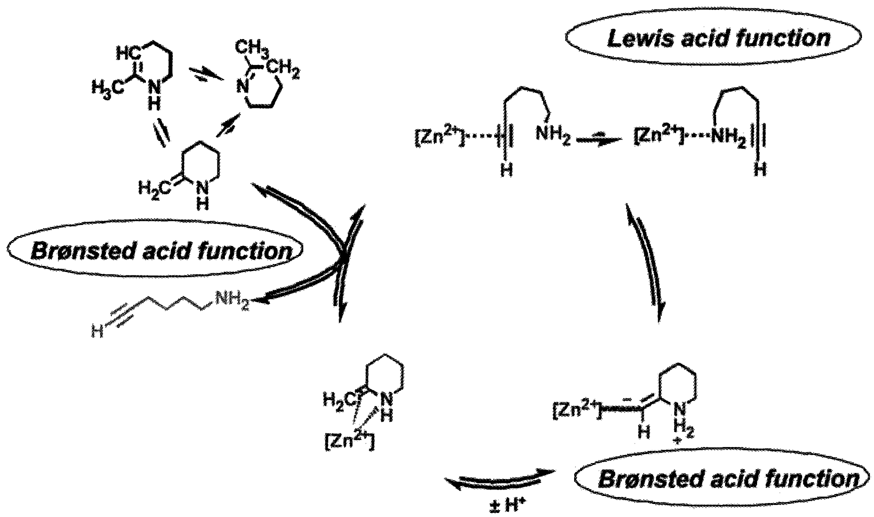

Figure 2. Mechanism proposed for the cyclisation of 6-aminohex-1-yne on zinc catalysts.

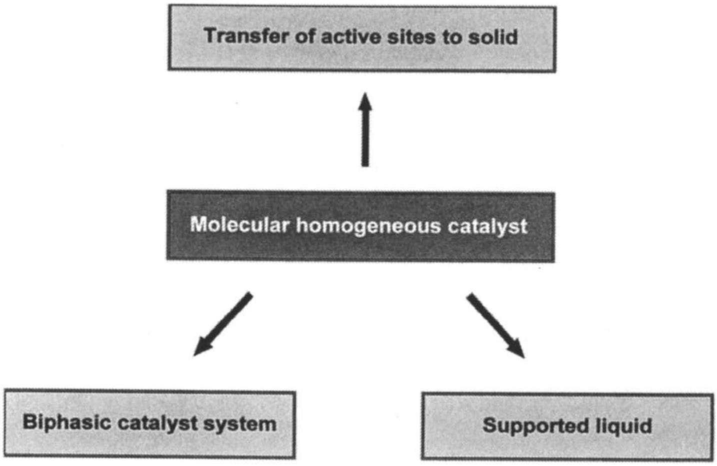

Figure 3. Approaches for modification of homogeneous catalyst to enable catalyst separation in continuous operation.

Results and Discussion

In the traditional approach to heterogeneous catalysts, the active site present in the homogeneous catalyst is transferred onto the surface of a solid material. We have explored this concept by immobilising Lewis acidic metal centres in zeolite Beta. Especially H-Beta exchanged with Cu^+, Rh^+ and Zn^{2+} ions showed a high catalytic activity in the cyclisation of 6-aminohex-1-yne (5). Most noteworthy, the strong dependence of the catalytic activity on the nature of the cation was similar to homogeneous catalysis. Apparently, an optimum Lewis acid strength is necessary to catalyse the reaction efficiently in agreement with the Sabatier principle (Figure 4). Further, ion exchanged Zn-H-Beta had exactly the same catalytic activity as $Zn(CF_3SO_3)_2$/ CF_3SO_3H in a ratio 1:100 which strongly suggested that also in the heterogeneous case the reaction is co-catalysed by Lewis-acidic metal cations and Brønsted acid sites.

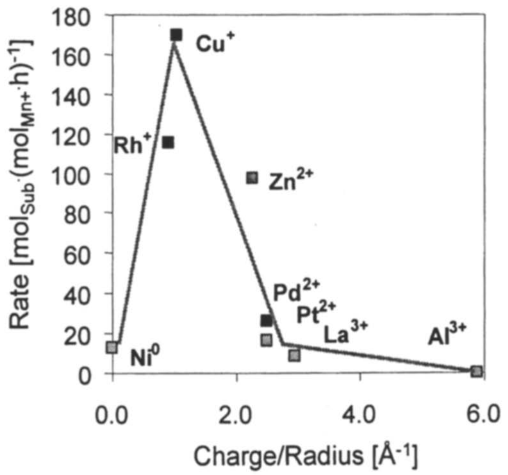

Figure 4. Catalytic activity of ion exchanged zeolite Beta in the cyclisation of 6-aminohex-1-yne.

As alternative approach we have immobilised the homogeneous metal complexes in a second liquid phase (6). To maintain the Lewis acidity of the metal complexes a non-coordinating solvent with sufficient mixability gap to a non-polar solvent (heptane) for dissolution of the substrate and product, respectively, was required. Therefore we have chosen the ionic liquid 1-ethyl-3-methylimidazolium trifluoromethanesulphonate ($EMIM^+$ $CF_3SO_3^-$) as solvent for the catalyst. A surprisingly high catalytic activity for the cyclisation of 6-aminohex-1-yne was observed in a preliminary experiment after a couple of drops of $EMIM^+$ $CF_3SO_3^-$ had been added to a homogeneous reaction mixture

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with $Zn(CF_3SO_3)_2$ as catalyst and toluene as solvent for 6-amino-hex-1-yne (Figure 5).

Similar high catalytic activities were observed also with other organic solvents. Analysis of the organic phase in the biphasic system heptane / $EMIM^+$ $CF_3SO_3^-$ with AAS proved that the Zn^{2+} salt had been immobilised very efficiently in the ionic liquid. For optimisation of biphasic reaction systems it is very important to identify whether the reaction occurs at the phase boundary or in one of the bulk phases. Three observations on this reaction system are important in this respect. (i) *In situ* NIR spectroscopy showed that neither substrate nor product diffused into the ionic liquid phase. (ii) The rate of reaction was directly proportional to the area of the reacting interface. (iii) The apparent activation energy was determined to $E_a = 28 \pm 8$ kJ·mol^{-1} which is very low for hydroamination reactions but would be more consistent with a diffusion limited reaction. These observations strongly suggest that the cyclisation of 6-aminohex-1-yne occurs at the phase boundary.

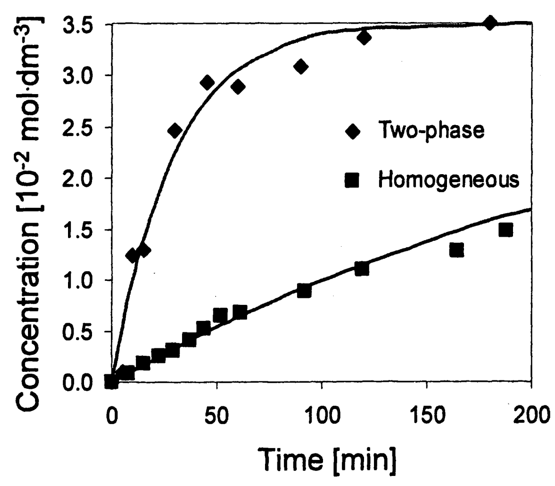

Figure 5. Comparison of the time-concentration profiles for the formation of (4-isopropyl-phenyl)-(1-phenylethylidene)-amine in the cyclisation of 6-aminohex-1-yne with $Zn(CF_3SO_3)_2$ with and without added $EMIM^+$ $CF_3SO_3^-$.

The biphasic reaction system was then tested for the intermolecular addition of 4-isopropyl-phenylamine to ethynyl-benzene (Equation 2) (7). The reaction provides (4-isopropylphenyl)-(1-phenyl-vinyl)-amine as intermediate product which isomerises *in situ* to the imine (4-isopropyl-phenyl)-(1-phenylethylidene)-amine.

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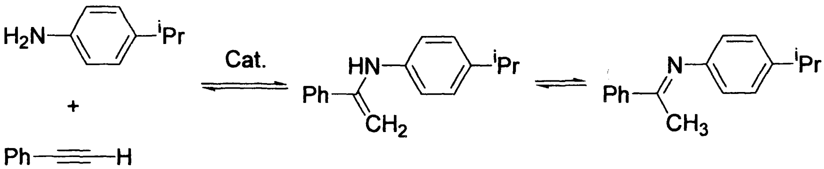

(2)

Following the course of the reaction with time showed an initial rapid decrease in the concentration of 4-isopropyl-phenylamine and ethynyl-benzene in the heptane phase whereas the product was formed according to second order kinetics (Figure 6). In consequence, the mass balance in the heptane phase was not closed with a minimum of 90% after about 30 min. This strongly suggested that at the start of the reaction the reactants rapidly dissolved in the ionic liquid phase. In deed, the partitioning coefficient of 4-isopropyl-phenylamine and ethynyl-benzene between $EMIM^+$ $CF_3SO_3^-$ and heptane were large with 5.2 and 7.2, respectively (384 K). In contrast, the product was hardly soluble in the ionic liquid. This clearly shows that the reaction occurred in the bulk ionic liquid. The high solubility of the reactants in the ionic liquid provides a high concentration in the vicinity of the catalyst whereas the product readily diffuses back into the organic phase. In consequence, the reaction equilibrium is shifted to formation of the products.

To utilize the differences in solubility and in order to combine the advantages of homogeneous and solid catalysts, we decided to support the catalyst

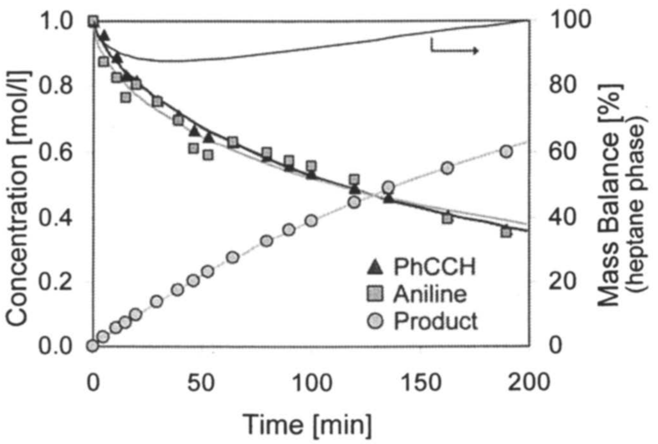

Figure 6. Time-concentration profile for the addition of 4-isopropyl-phenylamine to ethynyl-benzene in the bi-phasig system comprising a substrate/product phase in heptane and a catalyst phase of $Zn(CF_3SO_3)_2$ in $EMIM^+$ $CF_3SO_3^-$.

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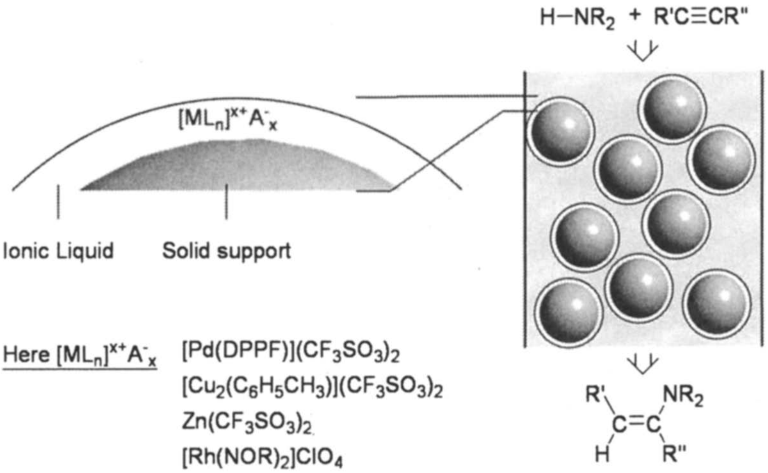

Figure 7. Concept for the immobilisation of organometallic complexes in a supported film of ionic liquid. (Adapted with permission from reference 7.)

solution as thin film on a solid material. The concept is shown schematically in Figure 7. The goals were (i) to provide a new method for easily transferable immobilization of organometallic complexes and (ii) to enhance the reaction rate by optimizing the adsorption and desorption process.

For preparation of the catalysts, saturated solutions of the homogeneous complexes $Zn(CF_3SO_3)_2$, $[Pd(DPPF)](CF_3SO_3)_2$ (DPPF = 1,1'-*bis*-di-phenyl-phosphino-ferrocene), $[Rh(NOR)_2]ClO_4$ and $[Cu_2(C_6H_5CH_3)](CF_3SO_3)_2$ in $EMIM^+$ $CF_3SO_3^-$ were supported on diatomic earth. Latter was chosen as it is used as packing material for supported liquid films in gas chromatography applications. Although the final material contained up to 10 wt% ionic liquid, the catalysts were dry and well flowing powders. Figure 8 shows a SEM micrograph of the supported zinc catalyst with 9.5 wt% IL and 5.7 wt% $Zn(CF_3SO_3)_2$. The diameter of the particles was in the range 180–250 μm and provided smaller pores with 0.9 μm mean diameter. By the presence of a liquid film with average 20 nm thickness the surface area was reduced from 10 m^2/g to 4.9 m^2/g.

Most noteworthy, the catalytic activity of the supported catalyst in the addition of the 4-isopropyl-phenylamine to ethynyl-benzene was generally higher than of the corresponding homogeneous catalyst (Table 1). The catalytic activity was increased by a factor of 5.8 for the zinc complex, 2.05 and 2.12 for the palladium and rhodium complexes respectively. In parallel the selectivity to the hydroamination product was increased significantly. The copper complex constituted an exception in that the catalytic activity of the supported catalyst was much lower than of the homogeneous catalyst. However, this can be readily explained with a strong complexation of the Cu^I cations by the imidazolium cation which prevents approach of the substrate to the cation.

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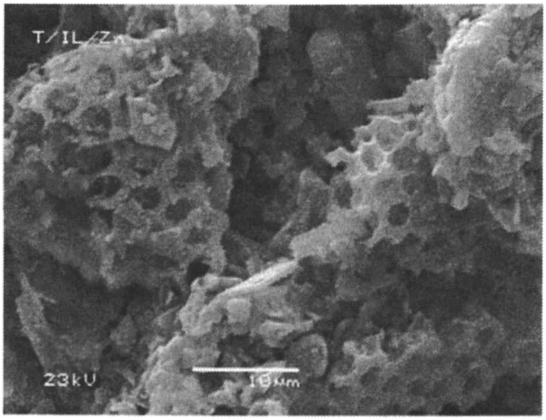


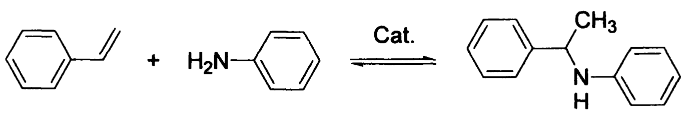
Figure 8. SEM micrograph of the catalyst particles with $Zn(CF_3SO_3)_2$ immobilized in a thin film of $EMIM^+$ $CF_3SO_3^-$ on diatomic earth.

Table 1. Initial catalytic activity of supported catalysts with immobilised organometallic complexes in comparison to the corresponding homogeneous reaction (at 98°C).

Metal complex	Initial activity mol·$(mol_{cat}·h)^{-1}$	
	Homogeneous	Supported catalyst
$Zn(CF_3SO_3)_2$	0.10	0.58
$[Pd(DPPF)](CF_3SO_3)_2$	2.10	4.30
$[Cu_2(C_6H_5CH_3)](CF_3SO_3)_2$	17.0	0.83
$[Rh(DPPF)(NOR)]ClO_4$	0.34	0.72

In summary, the supported catalysts combine a higher catalytic activity with an increase in selectivity which makes yields of up to 100% possible.

Can the concept be transferred to intermolecular hydroamination of alkenes? Recently, Kawatsura and Hartwig described a similar catalyst system comprising $Pd(CF_3CO_2)_2$, DPPF, CF_3SO_3H in a molar ratio 2:3:20 for the addition of aniline to vinyl-benzene (Equation 3) (8). To systematically study the effect of the ionic



(3)

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liquid, twelve different supported catalysts were prepared varying in palladium concentration (0, 0.011, 0.022 and 0.042 mmol·g^{-1}) and choice of the 1-alkyl-3-methylimidazolium salt. By changing the substituent from alkyl = ethyl to butyl and hexyl, the polarity of the ionic liquid was systematically changed from relatively polar to quite non-polar. As inert support flame dried silica with a surface area of 150 m^2/g and a particle size of 60-200 μm was chosen. Figure 9 shows SEM micrograph of supported catalysts. Even at a very high magnification the ionic liquid film with average 3 nm thickness can not be distinguished.

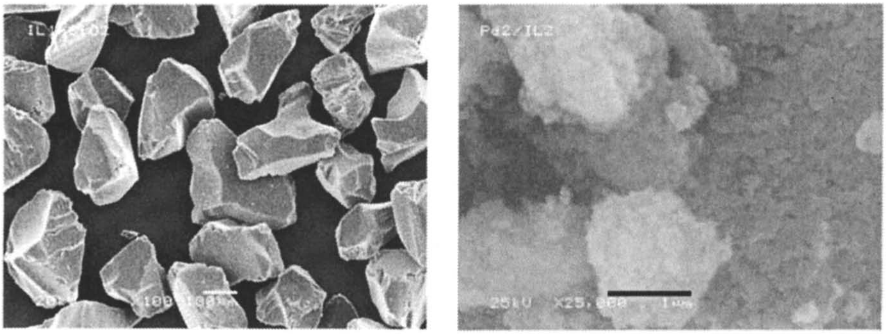

Figure 9. SEM micrographs of the supported silica catalyst with CF_3SO_3H immobilised in $BMIM^+$ $CF_3SO_3^-$ (left, 0.22 $mmol_{CF_3SO_3H}g_{Cat}^{-1}$) and an in situ mixture of $Pd(CF_3CO_2)_2$, DPPF and CF_3SO_3H immobilised in $BMIM^+$ $CF_3SO_3^-$ (right, Pd contents 0.022 $mmol_{Pd^{2+}}g_{Cat}^{-1}$).

The BET surface area was reduced to between 37 and 45 m^2/g for the supported catalysts. Detailed analysis of the BET isotherms showed that the pore volume associated with small pores only had decreased dramatically (Figure 10), whereas the pore size distribution remained nearly unchanged. The mean pore radius was slightly shifted from 9.3 nm to higher values (9.6 – 11.8 nm). These data would be consistent with the formation of a film with even thickness throughout the material. The volume of small pores would then be reduced significantly whereas the volume of larger pores would hardly be affected. In consequence, the pore diameter of every pore would be reduced by the thickness of the liquid film; however, the distribution of the remaining open pore space would be shifted towards larger pores.

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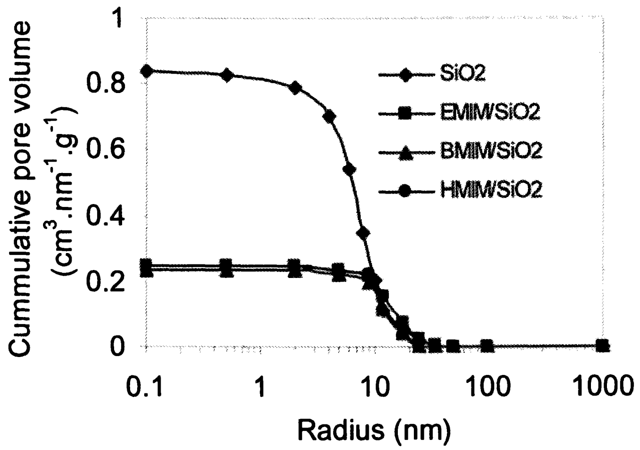

Figure 10. Cumulative pore volume and pore size distribution for the silica used in this study and supported ionic liquids.

IR spectra of the catalysts showed that the signal due to the silanol groups of the parent silica (at ca. 3745 cm^{-1}) disappeared upon treatment with the ionic liquid solution indicating strong hydrogen bonding interactions between support and thin film of ionic liquid (Figure 11). This conclusion is also supported by the presence of an intense very broad band in the spectra of the supported catalysts which is centred at 3300 cm^{-1}.

For all supported palladium catalysts the addition of aniline to vinylbenzene followed a second order regime. The catalytic activity increased with

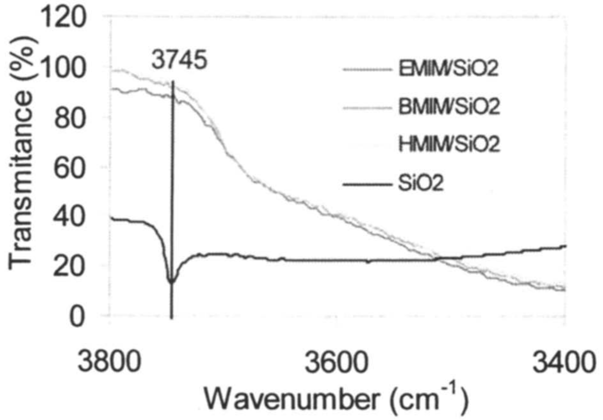

Figure 11. IR spectra of the supported catalysts in comparison to the parent silica.

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the palladium concentration in each series of catalysts (Figure 12). It is noteworthy that the ratio in activity expressed in mol·$(g_{cat}·h)^{-1}$ was roughly 1:2 for the catalyst with 0.022 and 0.042 $mmol_{Pd}{}^{2+}·g_{Cat}{}^{-1}$. In contrast, the activity of the catalyst with 0.011 $mmol_{Pd}{}^{2+}·g_{Cat}{}^{-1}$ was much lower than anticipated. Apparently there is a lower limit for the palladium concentration which would be consistent with strong adsorption of the palladium complexes on surface OH groups of the silica. This interaction would render part of the palladium complexes catalytically inactive. The reference samples which did not contain a palladium complex, but only CF_3SO_3H displayed no activity. With a molar ratio aniline / Pd^{2+} = 1904 for the catalyst with 0.042 $mmol_{Pd}{}^{2+}·g_{Cat}{}^{-1}$ supported in $[EMIM]^+$ $CF_3SO_3^-$ an average turnover frequency of TOF 24 h^{-1} and TON 580 is calculated for a period of 24 h. This compares to 99% yield after 7h reported for the homogeneous catalyst which is equivalent to TOF 7 h^{-1} and TON 50. When compared under equal reaction conditions, the catalytic activity of the immobilized catalysts slightly exceeds the activity of the corresponding homogeneous catalyst (Table 2). For all catalysts the selectivity was 100% on the basis of aniline and between 50 and 95% based on vinyl-benzene, mainly due to oligomerisation as side reaction.

Table 2. Comparison of the catalytic activity of the supported catalyst with the corresponding homogeneous and two phase catalysis.

Catalyst	Rate mol·(mol Pd^{2+}·h)$^{-1}$
Homogeneous	23.2
Two-Phase	32.2
Supported	33.3

Most noteworthy, the activity increased with the polarity of the ionic liquid, i.e. in the sequence alkyl = hexyl < butyl < ethyl. In their publication, Kawatsura and Hartwig had suggested two different mechanism for the reaction (5), one based on a nucleophilic attack (9) on a Л-coordinated vinyl-benzene similar to the mechanism described above for the cyclisation of 6-aminohex-1-yne and, second, a mechanism based on formation of a palladium hydride, ethene insertion and electrophilic attack of the amine group on the alkyl ligand. While former mechanism involves a 1,3-dipolar intermediate with charge separation (10), the polarisation of intermediates in the catalytic cycle is decreased in the latter. A highly polar environment – as provided by the ionic liquid – will stabilise polar intermediates and facilitate charge separation. Therefore, it is concluded that the data for the addition of aniline to vinyl-benzene are more consistent with nucleophilic attack of the amine on the Л-coordinated vinyl-benzene.

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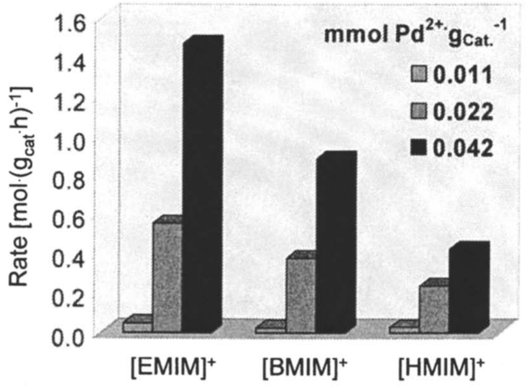

Figure 12. Catalytic activity of palladium complexes immobilized in a thin film of 1-alkyl-3-methyl-imidazolium trifluoromethanesulphonate on silica.

Last, but not least, the supported catalyst was tested for leaching of the active palladium complex. The catalyst suspension was filtered hot and the heterogeneous catalyst removed from the reaction mixture after 2 and 24 h, respectively. The reaction was then carried on, but no further conversion was observed (Figure 13). Thus, leaching of the palladium catalyst into the bulk organic phase did not seem to occur. AAS analysis confirmed the absence of palladium in the organic phase.

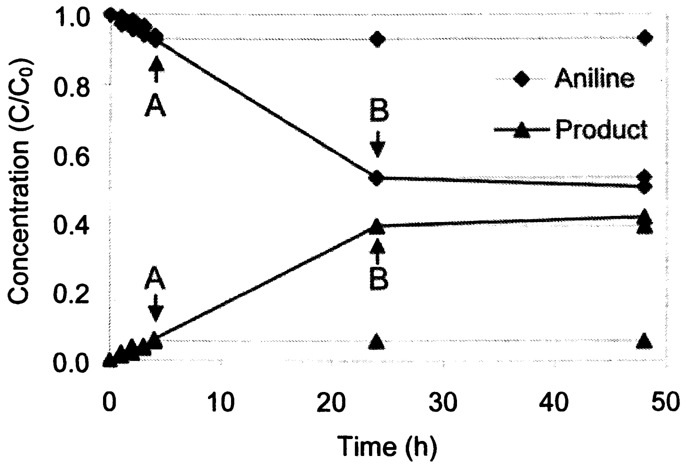

Figure 13. Time-concentration profiles during the leaching test in the palladium catalysed addition of aniline to vinyl-benzene. A and B indicate the times, when the catalyst was removed by filtration (after 4 and 24 h, respectively).

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Experimental

Catalyst preparation

Silica (aerosil 355, Degussa) with a particle size in the range 60-200 μm was used to support a thin film solution of palladium trifluoroacetate $Pd(CF_3CO_2)_2$, 1,1'-*bis*-diphenylphosphino-ferrocene (DPPF) and trifluoromethane sulphonic acid (TfOH) in 1-alkyl-3-methyl-1-H-imidazolium trifluoromethanesulphonate, alkyl = ethyl ($EMIM^+$ $CF_3SO_3^-$), butyl ($BMIM^+$ $CF_3SO_3^-$) and hexyl ($HMIM^+$ $CF_3SO_3^-$). The following procedure was adopted for the immobilization of homogeneous catalysts (Figure 14). $Pd(CF_3CO_2)_2$ and DPPF were dissolved in 50 ml dichloromethane (Solution 1). Trifluoromethane sulphonic acid was dissolved in 2.5 ml of the ionic liquid (Solution 2). Solution 1 was added to Solution 2 and stirred for 10 min. Silica (5 g) activated before at 200 °C in vacuum was added and the suspension stirred for 1 hour. Finally, the suspension was rapidly frozen and freeze-dried to give a well flowing orange powder. For comparison reasons, a further series of samples was prepared in the same way with TfOH, but without addition of a metal catalyst.

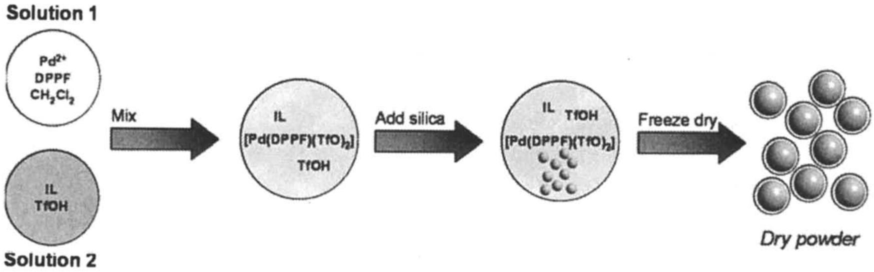

Figure 14. Experimental procedure for the preparation of catalysts with supported ionic liquids ($ML_n^{x+}A_x^-$ organometallic complex).

Catalytic experiments

The supported catalyst was tested in suspension for activity in the addition of aniline to vinyl-benzene. Catalytic experiments were performed in an inert atmosphere of nitrogen using a 12-fold batch reactor. The catalysts (0.25 g) were suspended in octane (15 cm^3) and heated to reflux at 125°C. Aniline (1.82 ml, 20 mmol), vinyl-benzene (3.44 ml, 30 mmol) and undecane (1 ml, internal GC standard) were added to each reactor. Samples (100 μl) of the liquid phase were taken periodically and analyzed by gas chromatography (GC). In order to test the catalyst for leaching reaction mixtures prepared in same way as described above were filtered hot after 4 and 24 h, respectively. The filtrate was kept at reflux and further samples were taken after 24 h total reaction time.

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Conclusions

In the present work, we compared three different concepts for the immobilisation of cationic late transition metal complexes. Especially the immobilisation of homogeneous catalysts in a thin film of supported ionic liquid combines advantages of homogeneous catalysis (optimum utilisation of metal centres, such as high selectivity) with those of heterogeneous catalysis (facile recovery of catalyst, application in continuous processes). We have shown the practicability of the concept for the addition of amines to alkynes and alkenes where Lewis acidic metal complexes (based on metal cations such as Zn^{2+} and Pd^{2+}) are excellent catalysts. The complexes can very efficiently be immobilised in the ionic liquid and no leaching was observed. The reaction is accelerated in the presence of protons which function as co-catalyst.

In summary, the concept of immobilizing homogeneous catalysts in a thin film of ionic liquid has been proven as functional. It is especially noteworthy that the concentration of reactants and products in the ionic liquid phase is different from those in the bulk organic phase. This effect can be utilized to locally change concentrations in the vicinity of the catalytically active metals centres and, thereby, direct reaction thermodynamics. Due to their tuneable acidity and polarity, ionic liquids are particularly favourable for this application. Their appropriate selection allows to influence adsorption properties and, in consequence, catalytic activity, selectivity and chemical equilibrium. Generalised, this concept provides one of the few methods for directing thermodynamic equilibria.

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Chapter 22

Synthesis and Application of New Ionic Liquids with Tris(perfluoroalkyl)trifluorophosphate Anions

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The synthesis of new ionic liquids with tris(perfluoroalkyl)-trifluorophosphate (FAP) anions is described. The physico-chemical properties of this new generation of ionic liquids are discussed. FAP ionic liquids show an excellent hydrolytic stability, low viscosity and high thermal stability, that makes them attractive for the application as new reaction media in organic synthesis.

1. Introduction.

Ionic Liquids are the modern approach to replace volatile and flammable organic compounds, which are used as solvents in organic synthesis. The application of ionic liquids as novel reaction media may have a grate impact on the future development of chemical technologies and chemical engineering (1). Ionic liquids as novel reaction media have a clear advantages in comparison to traditional organic solvents. They are not volatile and not flammable. The properties of ionic liquids (thermal and electrochemical stability, viscosity and solution-ability) can be tuned simply by the variation of the cation-anion pair. But, ionic liquids are still relatively expensive. From this point of view, the application of ionic liquids as reaction media makes sense if the yield, quality of the product or efficiency of an expensive catalyst is greatly improved. Ionic liquids can also make an improvement in the process if the product isolation is simplified and ionic liquids themselves can be reused several times without substantial loosing of the process efficiency.

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Both of these approaches are reasonable, but in the case of continued use of ionic liquids their lifetime is a crucial point. Long-term applicability of ionic liquids is directly related to their thermal and hydrolytical stability. First (tetrachloroaluminates) and second (tetrafluoro-borates and hexafluorophosphates) generations of ionic liquids are moisture sensitive. Commonly used ionic liquids with hexafluorophosphate, $[PF_6]^-$ anion are hydrolytically unstable, especially at elevated temperature (2). To address this disadvantage of the hexafluorophosphate anion, the replacement of some fluorine atoms by hydrophobic perfluoroalkyl-groups looks promising to increase the hydrolytic stability of fluorophosphates.

2. Results and Discussion.

2.1. Synthesis of ionic liquids with FAP – anion.

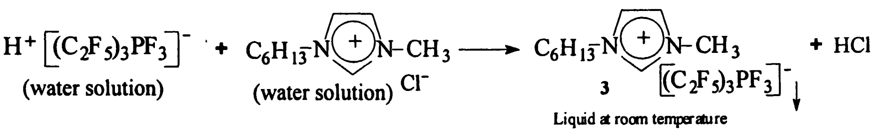
Recently Merck KGaA (Darmstadt, Germany) has developed convenient synthesis of ionic liquids with tris(perfluoroalkyl)trifluorophospate (FAP) -anion (water insoluble) (3,4)], as replacement for hydrolytically unstable PF_6^-.

Preparation of the ionic liquids with FAP – anion is based on the industrial process - electrochemical fluorination of trialkylphosphines, resulting in the formation of tris(perfluoroalkyl)difluorophosphoranes of type **1** in high yield (5).

$$(C_2F_5)_3PF_2 \qquad\qquad H^+ \left[(C_2F_5)_3PF_3\right]^- \cdot 5H_2O$$

1 **2**

Phosphoranes of type **1** can be easily converted into tris(perfluoroalkyl)-trifluorophosphoric acid (HFAP) of type **2** by the action of HF in water or in organic solvents [4]. Acid **2** is the new strong acid which shows better hydrolytic stability in comparison to HPF_6 and serves as convenient starting material for the synthesis of various salts with tris(perfluoroalkyl)-trifluorophosphate anion (FAP-anion), for example (Scheme 1) [4]:



Scheme 1

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2.2. Typical procedure for the preparation of ionic liquids with FAP-anion.

5.02 mol of tris(pentafluoroethyl)trifluorophosphoric acid pentahydrate, $H[(C_2F_5)_3PF_3] \cdot 5H_2O$, were added at room temperature to the stirred solution of 5.0 mol of N,N′-dialkylimidazolium chloride in 1.5 liter of water. The mixture was left stirring for 0.5 hour. The bottom phase was separated and washed with water until pH 6-7 and the test on chloride with silver nitrate was negative. The residue was dried at reduced pressure of 10-20 Pa at 80° - 90° C within 10-20 hours. The yield of N,N′-dialkylimidazolium tris(pentafluoroethyl)trifluorophosphate (usually liquid) is close to quantitative.

3. Physico-Chemical Properties of Ionic Liquids with FAP-anion.

3.1. Hydrolytic stability of FAP-ionic liquids.

The FAP-ionic liquids are not mixable with water, but mixable with polar organic solvents. The water uptake (saturation with water) for these ionic liquids is much less then for the popular ionic liquids with the bis(trifluoromethylsulfonyl)imide-anion and more than ten time less in comparison to the commonly used ionic liquids with the $[PF_6]^-$ anion. That allows access to FAP-ionic liquids with a very low content of residual water, 10-15 ppm, or even less.

FAP ionic liquids show an excellent hydrolytic stability. For example, no HF formation was detected for 1-hexyl-3-methylimidazolium FAP after five hours in boiled water (data from QUILL, Queen's University, Belfast, UK).

3.2. Thermal stability.

Typically ionic liquids with FAP-anion are liquids at room temperature and show a low melting point (glass transition point), typically below –50° C (see Table 1). FAP Ionic liquids also possess a high thermal stability. The data in Table 1 show that imidazolium based ionic liquids with FAP-anion start to decompose at temperatures of above 280° C.

3.3. Viscosity.

Viscosity is a very important for the practical application. Ionic liquids are more viscous then conventional organic solvents. By this reason the kinetic of

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Table 1

Ionic Liquid	M.P., °C	Decomposition, °C
1-Ethyl-3-methylimidazolium FAP	- 37	300
1-Pentyl-3-methylimidazolium FAP	<- 50	300
1-Hexyl-3-methylimidazolium FAP	<- 50	290
1-Butyl-1-methylpyrrolidinium FAP	<- 50	250
O-Ethyl-tetramethyluronium FAP	32-34	220
S-Ethyl-tetramethylthiouronium FAP	<- 20	250

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chemical or electrochemical processes, controlled by diffusion, can be slower then in the conventional organic solvents. To make the chemical process more effective, the low viscosity ionic liquids are required. Table 2 presents the data, which demonstrate dramatic influence the nature of the anion on the viscosity of ionic liquids. For example, replacement of three fluorine atoms in the $[PF_6]^-$ anion with pentafluoroethyl groups drastically decreases the kinematic viscosity of imidazolium ionic liquids (see Table 2). Replacement of chloride anion in trihexyl(tetradecy)-phosphonium chloride with FAP anion reduced the kinematic viscosity from 2757 mm^2/s to 393 mm^2/s (at 20° C), in spite of essential increasing in the molecular weight.

4. Application FAP – Ionic Liquids in Organic Synthesis.

4.1. Heck Reaction.

The Heck coupling of diazonium salt to an olefin was chosen as the model reaction to test the different ionic liquids. The investigation was focused on the process development and scaling-up in the conversion of *p*-anisidine and 2-ethyl hexylacrylate to the sunscreen active agent octyl-4-methoxycinnamate (OCM).

Table 2

Ionic Liquid	Viscosity (20° C), mm^2/s
1-Hexyl-3-methylimidazolium Cloride	7453
1-Hexyl-3-methylimidazolium PF_6^-	548
1-Hexyl-3-methylimidazolium BF_4^-	195
1-Hexyl-3-methylimidazolium FAP	74
1-Hexyl-3-methylimidazolium Imide	44

At the first step a system was developed involving the transformation of aryl amines into diazonium salts. These salts are then used in Heck-type coupling with an olefin (Scheme 2).

The palladium catalyst used was either palladium(II) acetate (PdAc) or colloidal palladium (c-Pd), consisting of a polyvinylpyrrolidone support and containing 2.9 % palladium by weight.

Diazotisations were carried out in an ice water bath by dissolving 0.001 mol *p*-anisidine in 1 ml of an aqueous solution containing approximately 0.002 mol of either HBF4 or TFA. The *p*-anisidine solutions were placed in an ice bath (0 °C) and 0.5 ml of a 2.0 M aqueous solution of $NaNO_2$ were added to each. After 90 min, the diazonium salt was extracted into 1 ml of an ionic liquid solution containing 0.075 mmol of palladium (16.8 mg PdAc or 274 mg c-Pd). The aqueous phase was decanted and 4 ml of a 0.026 M solution of 2-ethylhexylacrylate (EHA) in 2-ethylhexanol (2-EH) to the ionic liquid phase. The effect of changing (i) the acid of diazotisation (HBF_4 versus TFA), (ii) the catalyst (PdAc versus palladium c-Pd) and (iii) the ionic liquid medium ([bmim][PF_6] versus [emim] [FAP]) were studied. Eight reactions were carried out simultaneously at 60 °C. 20 μl aliquots were periodically sampled for HPLC analysis for the first three hours and after eighteen hours.

The results of the HPLC analysis, showing the yield of OMC, are shown in Figure 1. It is easy to see that the use of TFA (solid symbols) is preferable to HBF_4 (open circles). In all cases, in both the rate of the initial reaction and the final yield of OMC, TFA outperforms HBF_4. It is also clear that the PdAc (dark symbols) and c-Pd (light symbols) performed equally well, at least with respect to initial rate with the c-Pd perhaps slightly outperforming PdAc with respect to

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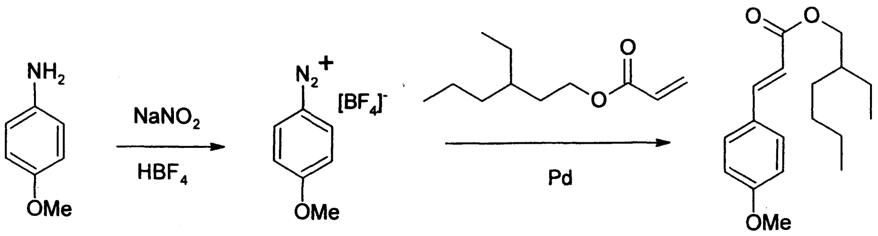

Scheme 2

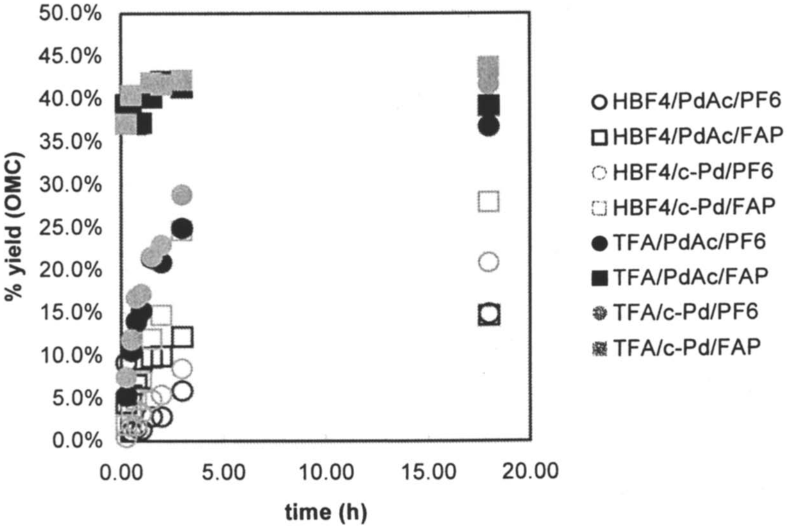

Figure 1. Synthesis of OMC. Effect of changes to acid of diazotisation, catalyst and ionic liquid.

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final yield. (Though this 'outperformance' is most likely within the error of margin.)

The effect of the ionic liquid upon the reaction is most striking: [emim][FAP] (squares) clearly shows an increased initial rate over the [bmim][PF_6] (circles) ionic liquids. A direct comparison of the reaction run under conditions used before and after optimization is shown in Figure 2.

These results show, that application of FAP – ionic liquids as reaction media in the synthesis of octyl-4-methoxycinnamate (OMC) via Heck reaction improves the yield of the final product and make the kinetics of the process faster.

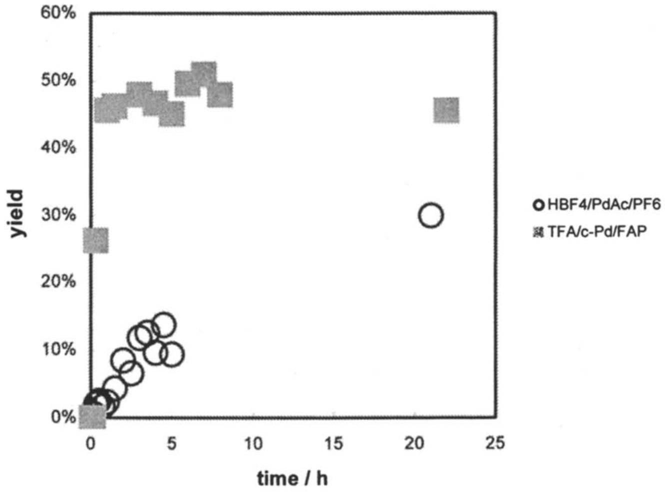

Figure 2. Synthesis of OMC. Optimization of the process.

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